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(54) THE: NOVEL BENZOTHEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSFORT AND TAUROCHOLATE UFTAKE

(57) Abstract

Provided are novel benzohlepines, derivatives, and analogo thereof; pharmaceuteal compositions comtaining them; and methods of using these compounds and compositions in nocitiene, particularly in the prophybasis and treament of hyperlipidemic conditions such as those associated with atheroacterosis or hyperholesterolemia, in mammals,

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## NOVEL BENZOTHIEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

This application claims the benefit of priority of U.S. Provisional Application No. 60/013,119, filed March 11, 1996, which is a continuation in part of U.S. Serial No. 08/\_\_\_\_, filed August 21, 1995, which is a continuation-in-part of U.S. Serial No. 08/305,526 filed September 12, 1994, both now pending.

#### BACKGROUND OF THE INVENTION

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#### Field of the Invention

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The present invention relates to novel benzothiepines, derivatives and analogs thereof, pharmaceutical compositions containing them, and their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as is associated with atherosclerosis or hypercholesterolemia, in mammals.

#### Description of Related Art

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It is well-settled that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly atherosclerosis. Interfering with the circulation of bile acids within the lumen of the intestinal tract is found to reduce the levels of serum cholesterol in a causal relationship. Epidemiological data has accumulated which indicates such reduction leads to an improvement in the disease state of

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atherosclerosis. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties," Biochimica et Biophysica Acta, 1210 (1994) 255-287 discusses the biochemistry, physiology and known active agents surrounding bile acids and cholesterol.

Pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic circulation of bile acids in humans by Heubi, J.E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport",

Gastroenterology, 1982:83:804-11.

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In fact, cholestyramine binds the bile acids in the intestinal tract, thereby interfering with their normal enterohepatic circulation (Reihnér, E. et al, in "Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-COA reductase activity and low density lipoprotein receptor expression in gallstone patients", Journal of Lipid Research, Volume 31, 1990, 2219-2226 and Suckling el al, "Cholesterol Lowering and bile acid excretion in the hamster with cholestyramine treatment", Atherosclerosis, 89(1991) 183-190). This results in an increase in liver bile acid synthesis by the liver using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol levels.

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In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with

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specific transport inhibitors (Kramer, et al,
"Intestinal Bile Acid Absorption" The Journal of
Biglogical Chemistry, Vol. 268, No. 24, Issue of August
25, pp. 18015-18046, 1993).

In a series of patent applications, eg Canadian Patent Application Nos. 2,025,294; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 379 161; 0 549 967; 0 559 064; and 0 563 731, Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including bile acid, which inhibit the physiological bile acid transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as hypocholesterolemic agents.

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In vitro bile acid transportinhibition is disclosed to show hypolipidemic activity in The Wellcome Foundation Limited disclosure of the world patent application number WO 91/16055 for "Hypolipidemic Benzothiazepine Compounds"

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Selected benzothiepines are disclosed in world patent application number WO93/321146 for numerous uses including fatty acid metabolism and coronary vascular

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Other selected benzothiepines are known for use as hypolipaemic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed by application Nos. EP 508425, FR 2661676, and WO 92/18462, each of which is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclo benzothiepine ring.

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The above references show continuing efforts to find safe, effective agents for the prophylaxis and treatment of hyperlipidemic diseases and their usefulness as hypocholesterolemic agents.

Additionally selected benzothiepines are disclosed for use in various disease states not within the present invention utility. These are EP 568 898A as abstracted by Derwent Abstract No. 93-351589; WO 89/1477/A as abstracted in Derwent Abstract No. 89-370688; U.S. 3,520,891 abstracted in Derwent 50701R-B; US 3,287,370, US 3,389,144; US 3,694,446 abstracted in Derwent Abstr. No. 65860T-B and WO 92/18462.

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The present invention furthers such efforts by providing novel benzothiepines, pharmaceutical compositions, and methods of use therefor.

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#### SUMMARY OF THE INVENTION

Accordingly, among its various apects, the present invention provides compounds of formula (I):

 $\Xi$ 

wherein:

q is an integer from 1 to 4; n is an integer from 0 to 2;

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R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

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wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of or NR\*\*9R\*10, N\*\*R\*\*PR\*\*A\*-, F\*R\*\*R\*\*A\*-, F\*R\*\*R\*\*A\*-, S(0)R\*9, S02R\*9 S03R\*9, C02R\*9, CN, halogen, oxo, and CONR\*\*9R\*10, wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl

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optionally have one or more carbons replaced by O, NR<sup>9</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>9</sup>A-, p<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, or phenylene,  $-9 \quad 10 \quad \text{3.5} \quad \text{3$ 

wherein  $R^9$ ,  $R^{10}$ , and  $R^w$  are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; or  $R^1$  and  $R^2$  taken together with the carbon to which

 $\rm R^3$  and  $\rm R^4$  are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle,  $\rm OR^9$ ,  $\rm NR^9R^{10}$ ,  $\rm SR^9$ ,  $\rm S(0)R^9$ ,  $\rm SO_2R^9$ , and  $\rm SO_3R^9$ , wherein R' and R' are as defined above; or

they are attached form C,-C, cycloalkylidene;

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 $\rm R^3$  and  $\rm R^4$  together form =0, =NOR  $^{11}$ , =5, =NNR  $^{11}\rm R^{12}$ , =NR  $^9$ , or =CR  $^{11}\rm R^{12}$ ,

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wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl,

cycloalkyl, cyanoalkyl,  $OR^9$ ,  $NR^9R^{10}$ ,  $SR^9$ ,  $S(0)R^9$ ,  $SO_2R^9$ ,  $SO_3R^9$ ,  $CO_2R^9$ , CN, halogen, oxo, and  $CONR^9R^{10}$ , wherein  $R^9$  and  $R^{10}$  are as defined above, provided that both  $R^3$  and  $R^4$  cannot be OH, NH2, and SH, or

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 $\rm R^{11}$  and  $\rm R^{12}$  together with the nitrogen or carbon atom to which they are attached form a cyclic ring;  $\rm R^5$  and  $\rm R^6$  are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl,

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cycloalkyl, heterocycle, quaternary heterocycle,  $\operatorname{OR}^9$ , SR<sup>9</sup>, S(0)R<sup>9</sup>, SO2R<sup>9</sup>, and SO3R<sup>9</sup>,

group consisting of alkyl, alkenyl, alkynyl, polyalkyl neteroaryl, halogen, oxo, OR $^{13}$ , NR $^{13}$ R $^{14}$ , SR $^{13}$ , S $^{(0)}$ R $^{13}$ SO2R<sup>13</sup>, SO3R<sup>13</sup>, NR<sup>13</sup>OR<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, NO2, CO2R<sup>13</sup>, CN, wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl polyether, aryl, haloalkyl, cycloalkyl, heterocycle, heterocycle, quaternary heterocycle, and quaternary substituent groups independently selected from the P(O)R<sup>13</sup>R<sup>14</sup>, P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R1SA-, P(OR")OR", S'R"R"A', and OM, SO2OM, SO2NR $^{13}$ R $^{14}$ , C(0)NR $^{13}$ R $^{14}$ , C(0)OM, COR $^{13}$ , heteroaryl can be substituted with one or more arylalkyl, quaternary heterocycle, quaternary N+R9R11R12A-,

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A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent  $conr^7 R^8$ ,  $n^+ R^7 R^8 R^9 A^-$ , alkyl, alkenyl, alkynyl, aryl. froups selected from the group consisting of  $\mathtt{OR}^7$ ,  $^{NR}^{7}R^{9}$ ,  $^{SR}$ ,  $^{S}$ cycloalkyl, heterocycle, arylalkyl, quaternary said alkyl, alkenyl, alkynyl, polyalkyl, heterocycle, quaternary heteroaryl,  $P(0)R^7R^8$ , 2 + R 7 R 8 R 9 A -, and P(O) (OR 7) OR 8, and

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polyether, aryl, haloalkyl, cycloalkyl, and heterocycle wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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can optionally have one or more carbons replaced by 0, NR7, N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>7</sup>A-, PR<sup>7</sup>, P(O)R7,

independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, quaternary heterocycle, quaternary heteroaryl, and P+R<sup>R</sup>A-, or phenylene, and R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are arylalkyl, cycloalkyl, heterocycle, heterocycle, quaternary heteroarylalkyl,

5 + 8 A, pR , p + 8 + 10 A -, P(0) R', phenylene, carbohydrate heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR\*, N\*R\*R<sup>10</sup>A~, S, SO, SO<sub>2</sub>, wherein alkyl, alkenyl, alkynyl, arylalkyl, amino acid, peptide, or polypeptide, and

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SO2NR9R10, PO(OR16)OR17, P'R9R10A-, S'R9A-, and C(O)OM. SO2R<sup>9</sup>, SO3R<sup>9</sup>, oxo, CO2R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO2OM R13, R14, and R15 are optionally substituted with one or more groups selected from the group consisting  $^{+}$ heteroaryl, OR $^{9}$ , NR $^{9}$ R $^{10}$ , N $^{+}$ R $^{9}$ R $^{11}$ R $^{12}$ A $^{-}$ , SR $^{9}$ , S(O)R $^{9}$ , of sulfoalkyl, quaternary heterocycle, quaternary

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from the substituents constituting  ${ t R}^9$  and  ${ t M}$ , and  ${ t p}$  is 0wherein R<sup>16</sup> and R<sup>17</sup> are independently selected

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 $\mathrm{R}^{14}$  and  $\mathrm{R}^{15}$ , together with the nitrogen atom to which they are attached, form a cyclic ring;

R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen and alkyl; and

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one or more RX are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,

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peptide, polypeptide, and carbohydrate,  $NR^{18}OR^{14}$ ,  $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  $P^{+}R^{9}R^{11}R^{12}A^{-}$ , amino acid. NR14C(0)R13, C(0)OM,  $COR^{13}$ ,  $OR^{18}$ ,  $S(0)_{D}NR^{18}$ ,  $NR^{13}_{R}$ 18, CN, OM, SO20M, SO2NR  $^{13}$ R  $^{14}$ , NR  $^{"}$ C(0)R  $^{"}$ , C(0)NR  $^{13}$ R  $^{14}$ SO3R13, S+R13R14A-, NR13OR14, NR13NR14R15, NO2, CO2R13, polyether, quaternary heterocycle, quaternary heteroaryl,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(O)R^{13}$ ,  $S(O)_2R^{13}$ haloalkyl, cycloalkyl, heterocycle, heterocycle, polyalkyl, acyloxy, aryl, arylalkyl, halogen,

 $P^{+}R^{9}R^{11}R^{12}A^{-}$ , S'R'R''A', or C(0)0M, and CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, PO(OR")OR"  $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  $SR^{9}$ ,  $S(0)R^{9}$ ,  $SO_{2}R^{9}$ ,  $SO_{3}R^{9}$ , oxo,  $CO_{2}R^{9}$ , polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with oR9, NR9R10 polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

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heterocycle, and alkyl, of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, wherein  $\mathbb{R}^{18}$  is selected from the group consisting

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 $SO_2OM$ ,  $SO_2NR^9R^{10}$ ,  $PO(OR^{16})OR^{17}$ , and C(O)OMSO2R<sup>9</sup>, SO3R<sup>9</sup>, oxo, CO2R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO3R<sup>9</sup> with one or more substituent selected from the group consisting of  $OR^9$ ,  $NR^9R^{10}$ ,  $N^+R^9R^{11}R^{12}A^-$ ,  $SR^9$ ,  $S(0)R^9$ , and quaternary heteroaryl optionally are substituted heterocycle, heterocycle, alkyl quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl

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replaced by 0,  $NR^{13}$ ,  $N^+R^{13}R^{14}A^-$ , s, s0,  $SO_2$ ,  $S^+R^{13}A^$ wherein in RX, one or more carbons are optionally

peptide, polypeptide, carbohydrate, polyether, or  $pR^{13}$ , P(0)R13,  $p+R^{13}R^{14}A-$ , phenylene, amino acid,

peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR $^9$ , N $^\dagger$ R $^1$ 0A-SO, SO2, S+R9A-, PR9, P+R9R10A-, or P(0)R', wherein in said polyalkyl, phenylene, amino acid,

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groups selected from the group consisting of alkyl,  $NR^{13}OR^{14}$ ,  $NR^{13}NR^{14}R^{15}$ ,  $NO_2$ ,  $CO_2R^{13}$ , CN, OM,  $SO_2OM$ , haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, alkenyl, alkynyl, polyalkyl, polyether, aryl, heteroaryl are optionally substituted with one or more OH, or SH and when  $\mathbb{R}^5$  is OH,  $\mathbb{R}^1$ ,  $\mathbb{R}^2$ ,  $\mathbb{R}^3$ ,  $\mathbb{R}^4$ ,  $\mathbb{R}^7$  and  $\mathbb{R}^8$  ${\tt P^+R^{13}R^{14}R15A^-,\ P(OR^u)OR^u,\ S'R^uR'A',\ and\ N^+R^9R^{11}R^{12}A^-}$  $SO_2NR^{13}R^{14}$ , C(0)NR<sup>13</sup>R<sup>14</sup>, C(0)OM, COR<sup>13</sup>, P(0)R<sup>13</sup>R<sup>14</sup> oxo, OR13, NR13R14, SR13, S(O)R13, SO2R13, SO3R13, cannot be all hydrogen; wherein quaternary heterocycle and quaternary provided that both  ${\tt R}^{\sf S}$  and  ${\tt R}^{\sf G}$  cannot be hydrogen,

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or R' is H; provided that when R' or R' is phenyl, only one of ୪

anilido, or anilinocarbonyl, only one of R' or R' is alkyl; or provided that when q = 1 and R is styryl

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prodrug thereof a pharmaceutically acceptable salt, solvate, or

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Preferably,  $R^5$  and  $R^6$  can independently be selected from the group consisting of H, aryl, heterocycle, quaternary heterocycle, and quaternary neteroaryl,

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR<sup>7</sup>, N<sup>+</sup>R<sup>8</sup>A-, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>7</sup>A-, PR<sup>7</sup>, P(0)R7, P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-, or phenylene,

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR<sup>7</sup>, NR<sup>7</sup>R<sup>8</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO2R<sup>7</sup>, CO2R<sup>7</sup>, CN, Oxo, CONR<sup>7</sup>R<sup>8</sup>, N<sup>4</sup>R<sup>7</sup>R<sup>8</sup>P<sub>8</sub>A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, P(O)R<sup>7</sup>R<sup>8</sup>, P<sup>4</sup>R<sup>7</sup>R<sup>8</sup>, p<sup>4</sup>R<sup>7</sup>R<sup>8</sup>, and P(O)(OR<sup>7</sup>OR<sup>8</sup>)

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More preferably, R' or R' has the formula:

-Ar-(R'),

wherein:

t is an integer from 0 to 5;

Ar is selected from the group consisting of phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, triazolyl, benzothiazolyl, and benzoimidazolyl; benzoxazolyl; and benzoisothiazolyl;

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one or more  $R^Y$  are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle,  $OR^9$ ,  $SR^9$ ,  $S(O)R^9$ , and  $SO3R^9$ ,

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wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocycle can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, SR<sup>13</sup>, S(O)R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, NR<sup>13</sup>OR<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, NO<sub>2</sub>, CO<sub>2</sub>R<sup>13</sup>, CN OM, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, C(O)NR<sup>13</sup>R<sup>14</sup>, C(O)OM, COR<sup>13</sup>, P(O)R<sup>13</sup>R<sup>14</sup>, P<sup>1</sup>R<sup>13</sup>R<sup>14</sup>R15A-, P(OR')OR', S'R'R'A, and NA<sup>13</sup>R<sup>14</sup>, P<sup>1</sup>R<sup>13</sup>R<sup>14</sup>R15A-, P(OR')OR', S'R'R'A, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR<sup>7</sup>, N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>7</sup>A-, PR<sup>7</sup>, P(0)R<sup>7</sup>, P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-, or phenylene.

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and P(O) (OR') OR', and

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Most preferably,  $R^5$  or  $R^6$  has the formula (II):

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The invention is further directed to a compound selected from among:

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$$R^{20} - R^{13} - R^{21}$$
 (Formula DI)

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 $R^{20} - R^{11} - R^{21}$  (Formula DII),

and

 $R^{2i} - R^{1i} - R^{2i}$  (Formula DIII)

wherein R" is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can optionally have one or more carbon atoms replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, phenylene, heterocycle, quatarnary heteroaryl, or aryl,

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wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkane diyl, carbohydrate, amino acid, peptide, and polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, SR<sup>13</sup>, S(0)R<sup>13</sup>, SO2R<sup>13</sup>, SO3R<sup>13</sup>, NR<sup>13</sup>OR<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, NO2, CO2R<sup>13</sup>, CN, OM, SO2OM, SO2NR<sup>13</sup>R<sup>14</sup>, C(O)NR<sup>13</sup>R<sup>14</sup>, C(O)OM, COR<sup>13</sup>, P(O)R<sup>13</sup>R<sup>14</sup>, P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R15A-, P(OR<sup>1)</sup>OR<sup>11</sup>, S'R<sup>1</sup>R<sup>1</sup>A, and N<sup>1</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>;

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by which R" is bonded to R", R", or R" in the compounds therapeutically effective in inhibiting ileal bile acid wherein R" further comprises functional linkages Formula DIII. Each of R", R", or R" and R" comprises of Formulae DII and DIII, and R" in the compounds of benzothiepine moiety as described above that is transport.

selected from among Formula DI, Formula DiI and Formula DIII in which each of R", R", R" and R" comprises a benzothiepine moiety corresponding to the Formula: The invention is also directed to a compound

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wherein R', R', R', R', R', R', R', G, and n are as defined in Formula I as described above, and R" is either a covalent bond or arylene.

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preferred that each of R", R", and R" in Formulae DII and DIII, and  $R^{11}$  in Formula DIII, be bonded at its 7-In compounds of Formula DIV, it is particularly

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or 8-position to R". In compounds of Pormula DIVA, it is particularly preferred that R" comprise a phenylene moiety bonded at a m- or p-carbon thereof to R"

Examples of Formula DI include:

and

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combinations the present invention can be used alone or in various discussed immediately above, benzothiepine compounds of In any of the dimeric or multimeric structures

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and R' can be ethyl/butyl or butyl/butyl. In any of the compounds of the present invention,

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to reduce transport thereof across digestive system effective to reduce bile acid levels in the blood, or disclosed above, alone or in combination, in an amount Such compositions comprise any of the compounds a pharmaceutical composition for the prophylaxis or excipient, or diluent membranes, and a pharmaceutically acceptable carrier hyperlipidemic condition, for example, atherosclerosis. acid transport inhibitor is indicated, such as a treatment of a disease or condition for which a bile In another aspect, the present invention provides

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provides a method of treating a disease or condition in In a further aspect, the present invention also 20

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dosage form or in divided doses. of the present invention in an effective amount in unit administering to a patient in need thereof a compound transport inhibitor is indicated, comprising mammals, including humans, for which a bile acid

also provides processes for the preparation of compounds of the present invention. In yet a further aspect, the present invention

understood that the following detailed dscription and description provided below. However, it should be scope of the invention will beomce apparent to those various changes and modifications within the spirit and invention, are given by way of illustration only since examples, while indicating preferred embodiments of the invention will become apparent from the detailed skilled in the art from this detailed description. Further scope of the applicability of the present

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### DETAILED DESCRIPTION OF THE INVENTION

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of the present inventive discovery. discussed herein can be made by those of ordinary skill not be construed to unduly limit the present invention aid those skilled in the art in practicing the present in the art without departing from the spirit or scope as modifications and variations in the emobodiments invention. Even so, this detailed description should The following detailed description is provided to

within these primary references, are herein herein, including the contents of the references cited incorporated by reference in their entirety. The contents of each of the references cited

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In order to aid the reader in understanding the following detailed description, the following definitions are provided: "Alkyl", "alkenyl," and "alkynyl" unless otherwise hydrocarbons of from one to twenty carbons for alkyl or ethenyl, propenyl, butenyl, pentenyl, or hexenyl and two to twenty carbons for alkenyl and alkymyl in the present invention and therefore mean, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and ethymyl, propymyl, butymyl, pentymyl, or hexymyl noted are each straight chain or branched chain respectively and isomers thereof.

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"Aryl" means a fully unsaturated mono- or multisubstituted or unsubstituted phenyl, naphthyl, or ring carbocyle, including, but not limited to, anthracenyl.

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carbon atoms can be replaced by N, S, P, or O. This "Heterocycle" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more includes, for example, the following structures:

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wherein Z, Z', Z" or Z"' is C, S, P, O, or N, with the carbon, but is not 0 or S when attached to another Z proviso that one of Z, Z', Z" or Z"' is other than

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understood to be attached to Z, Z', Z" or Z"' only when atom by a double bond or when attached to another 0 or S atom. Furthermore, the optional substituents are each is C.

The term "heteroaryl" means a fully unsaturated heterocycle. In either "heterocycle" or "heteroaryl," the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.

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The point of attachment for example, O, N, S, or P, has such a number of bonds heterocycle in which one or more of the heteroatoms, of the quaternary heterocycle to the molecule of The term "quaternary heterocycle" means a interest can be at a heteroatom or elsewhere. that it is positively charged.

heteroaryl in which one or more of the heteroatoms, for example, 0, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heteryaryl to the molecule of interest The term "quaternary heteroary1" means a can be at a heteroatom or elsewhere.

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The term "halogen" means a fluoro, chloro, bromo or iodo group. The term "haloalkyl" means alkyl substituted with one or more halogens.

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ten carbon atoms, and wherein any ring can contain one ringed carbocycle wherein each ring contains three to The term "cycloalkyl" means a mono- or multior more double or triple bonds.

said moiety has two points of attachment to molecules The term "diyl" means a diradical moiety wherein of interest.

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The term "oxo" means a doubly bonded oxygen

The term "polyalky1" means a branched or straight hydrocarbon chain having a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "polyether" means a polyalkyl wherein one or more carbons are replaced by oxygen, wherein the polyether has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

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The term "polyalkoxy" means a polymer of alkylene oxides, wherein the polyalkoxy has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "cycloaklylidene" means a mono- or multiringed carbocycle wherein a carbon within the ring structure is doubly bonded to an atom which is not within the ring structures.

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The term "carbohydrate" means a mono-, di-, tri-, or polysaccharide wherein the polysaccharide can have a molecular weight of up to about 20,000, for example, hydroxypropyl-methylcellulose or chitosan.

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The term "peptide" means polyamino acid containing up to about 100 amino acid units.

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The term "polypeptide" means polyamino acid containing from about 100 amino acid units to about 1000 amino acid units, more preferably from about 100 amino acid units to about 750 amino acid units, most preferably from about 100 amino acid units to about 500 amino acid units.

The term "alkylammoniumalkyl' means a NH, group o a mono-, di- or tri-substituted amino group, any of

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which is bonded to an alkyl wherein said alkyl is bonded to the molecule of interest.

The term "triazolyl" includes all positional isomers. In all other heterocycles and heteroaryls which contain more than one ring heteroatom and for which isomers are possible, such isomers are included in the definition of said heterocycles and heteroaryls.

The term "sulfoalkyl" means an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.

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The term "active compound" means a compound of the present invention which inhibits transport of bile acids.

When used in combination, for example "alkylaryl" or "arylalkyl," the individual terms listed above have the meaning indicated above.

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The term "a bile acid transport inhibitor' means a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system of a mammal, such as a human. This includes increasing the fecal excretion of bile acids, as well as reducing the blood plasma or serum concentrations of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid transport inhibition include, for example, a hyperlipidemic condition such as atherosclerosis.

#### Compounds

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The compounds of the present invention can have at least two asymmetrical carbon atoms, and therefore include racemates and stereoisomers, such as

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diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

Isomers may include geometric isomers, for example cis isomers or trans isomers across a double bond. All such isomers are contemplated among the compounds of the present invention.

The compounds of the present invention also include tautomers.

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The compounds of the present invention as discussed below include their salts, solvates and prodrugs.

#### Compound Syntheses

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The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

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Generally, the compounds of the present invention can be prepared by the procedures described below.

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For example, as shown in Scheme I, reaction of aldehyde II with formaldehyde and sodium hydroxide yields the hydroxyaldehyde III which is converted to mesylate IV with methansulfonyl chloride and triethylamine similar to the procedure described in Chem. Ber. 98, 728-734 (1965). Reaction of mesylate IV with thiophenol V, prepared by the procedure described in WO 93/16055, in the presence of triethylamine yields keto-aldehyde VI which can be cyclized with the

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reagent, prepared from zinc and titanium trichloride in refluxing ethylene glycol dimethyl ether (DME), to give a mixture of 2,3-dihydrobenzothiepine VII and two racemic steroisomers of benzothiepin-(5H)-4-one VIII when R' and R' are nonequivalent. Oxidation of VII with

3 equivalents of m-chloro-perbenzoic acid (MCPBA) gives isomeric sulfone-epoxides IX which upon hydrogenation with palladium on carbon as the catalyst yield a mixture of four racemic stereoisomers of 4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides X and two racemic stereoisomers of 2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides XI when R' and R' are nonequivalent.

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Optically active compounds of the present invention can be prepared by using optically active starting material III or by resolution of compounds X with optical resolution agents well known in the art as described in J. Org. Chem., 39, 3904 (1974), ibid., 42, 2781 (1977), and ibid., 44, 4891 (1979).

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Alternatively, keto-aldehyde VI where R' is H can be prepared by reaction of thiophenol V with a 2-substituted acrolein.

Benzothiepin-(5H)-4-one VIII can be oxidized with MCPBA to give the benzothiepin-(5H)-4-one-1,1-dioxide XII which can be reduced with sodium borohydride to give four racemic stereoisomers of X. The two stereoisomers of X, Xa and Xb, having the OH group and R' on the opposite sides of the benzothiepine ring can be converted to the other two isomers of X, Xc and Xd, having the OH group and R' on the same side of the benzothiepine ring by reaction in methylene chloride with 40-50% sodium hydroxide in the presence of a phase transfer catalyst (PTC). The transformation can also be carried out with potassium t-butoxide in THF.

R' = OR, NRR', S(O) R

MOH, PTCKH 2G2

shown in Scheme 2. Compound VI is oxidized to compound Another route to XC and Xd of the present invention is XIII with two equivalent of m-chloroperbenzoic acid. Hydrogenolysis of compound XIII with palladium on

carbon yields compound XIV which can be cyclized with either potassium t-butoxide or sodium hydroxide under Separation of Xc and Xd can be accomplished by either phase transfer conditions to a mixture of Xc and Xd.

HPLC or fractional crystallization.

The compounds of the present invention where R' is OR, NRR' and S(O) R and R' is hydroxy can be prepared by reaction of epoxide IX where R' is H with thiol, alcohol, and amine in the presence of a base.

whom R of Bu Ror Et R of Ph. X = 1, q = 4
68 = Xa
60 = Xa
60 = Xa
61 = Xa

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The thiophenols XVIII and v used in the present invention can also be prepared according to the Scheme 3. Alkylation of phenol XV with an arylmethyl chloride in a nonpolar solvent according to the procedure in J. Cham. 800., 2631-2632 (1958) gives the ortho substituted phenol XVI. The phenol XVI can be converted to the thiophenol XVIII via the thiocarbamate XVII by the procedure described in J. Org. Chem., 31, 3980 (1966). The phenol XVI is first reacted with dimethyl thiocarbamoyl chloride and triethylamine to give thiocarbamate XVII which is thermally rearranged at 200-300 °C, and the rearranged product is hydrolyzed with sodium hydroxide to yield the thiophenol XVIII. Similarly, Thiophenol V can also be prepared from 2-acylphenol XIX via the intermediate thiocarbamate XX.

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Scheme 4 shows another route to benzothiepine-1,1-dioxides Xc and Xd starting from the thiophenol XVIII. Compound XVIII can be reacted with mesylate IV to give the sulfide-aldehyde XXI. Oxidation of XXI with two equivalents of MCPBA yields the sulfone-aldehyde XIV which can be cyclized with potassium t-butoxide to a mixture of XC and Xd. Cyclyzation of sulfide-aldehyde with potassium t-butoxide also gives a mixture of benzothiepine XXIIC and XXIId.

hydrogenation of XXIV or XXVIIc and XXVIId.

sulfide followed by reacting the resulting sulfide with the hydroxylamine XXV. Protecting the hydroxylamine XXV aldehyde XXIV which can be reduced by hydrogenation to mesylate IV gives sulfide-aldehyde XXIII. Oxidation of compounds of the present invention can be prepared as Examples of amine- and hydroxylamine-containing nitrobenzophenone is reduced with triethylsilane and nitrodiphenylmethane 32. Reaction of 32 with lithium XXIII with 2 equivalents of MCPBA yields sulfonewith di-t-butyldicarbonate gives the N,O-di-(ttrifluoromethane sulfonic acid to 2-chloro-4shown in Scheme 5 and Scheme 6. 2-Chloro-4-

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reaction vessel yields the substituted amine derivative aldehyde catalyzed by palladium on carbon in the same resulting amino derivative with hydrogen and an with hydrogen followed by reductive alkylation of the In Scheme 6, reduction of the sulfone-aldehyde XXV

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yields a mixture of substituted amino derivatives of this invention XXIXc and XXIXd. XXVIII. Cyclization of XXVIII with potassium t-butoxide

palladium-catalyzed carbonylation in an alcohol yields triflate gives the iodo derivative XXXI, which upon derivative XXX with iodine catalyzed by mercuric position of benzothiepine. Iodination of 5-phenyl the carboxylate XXXII. Hydrolysis of the carboxylate introducing a substituent to the aryl ring at the 5-Scheme 7 describes one of the methods of

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and derivatization of the resulting acid to acid derivatives are well known in the art. Abbreviations used in the foregoing description have the following meanings:

THF---tetrahydrofuran

R D

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Aliquart 336---methyltricaprylylammonium chloride PTC---phase transfer catalyst

Celite--- a brand of diatomaceous earth filtering

MCPBA---m-chloroperbenzoic acid

aid

DMF --- dimethyl formamide

DME----ethylene glycol dimethyl ether

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BOC---t-butoxycarbonyl group

R' and R' can be selected from among substituted and unsubstituted C, to C, alkyl wherein the

substituent(s) can be selected from among

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alkylcarbonyl, alkoxy, hydroxy, and nitrogen-containing .nclude ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, heterocycles joined to the C, to C, alkyl through an ether linkage. Substituents at the 3-carbon can

picoline). Ethyl, n-propyl, n-butyl, and isobutyl are isopropyl, -CH,C(=0)C,H, -CH,OC,H, and -CH,O-(4-

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compounds of the present invention, substituents R' and preferred. In certain particularly preferred

R' are identical, for example n-butyl/n-butyl, so that the compound is achiral at the 3-carbon. Eliminating

selection, synthesis, separation, and quality control of the compound used as an ileal bile acid transport optical isomerism at the 3-carbon simplifies the

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unhibitor. In both compounds having a chiral 3-carbon and those having an achiral 3-carbon, substituents (R\*)

on the benzo- ring can include hydrogen, aryl, alkyl, hydroxy, halo, alkoxy, alkylthio, alkylsulfinyl,

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carboxyethylamino, (N)-morpholinyl, (N)-azetidinyl, dimethylamino, N, N-diethylamino, bromo, fluoro, methylsulfinyl, methylsulfonyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, iodo, and N-N'-methylpiperazinyl, (N)-bromomethylamido, (N)-(N)-N-methylpyridinium A', (N)-N-methylmorpholinium A', (N)-N-methylazetidinium A', (N)-pyrrolidinyl, pyrrolyl,  $-NHC (=0) CH_3$ ,  $-NHC (=0) C_3H_{11}$ ,  $-NHC (=0) C_4H_{13}$ , ethylthio, amino, hydroxylamine, N-methylamino, N,Nconstitute R\* are methyl, ethyl, isopropyl, t-butyl, (N)-benzyloxycarbamoyl, trimethylammonium, A quaternized. wherein the nitrogen of said heterocycle is optionally is 2 to 12, w is 2 or 3 and X is a halo or a quaternary ammonium salt substituted thereon,  $-[0(CH_j)_j]_-X$  where x substituents, an alkylene bridge having a quaternary ammonium salt, and (N)-nitrogen containing heterocycle trialkyl ammonium salt having a carboxylic acid or hydroxylamine, haloacylamine, carbohydrate, thiophene a acid, alkyl or benzyl ester, N-acylamine, carboxyalkyl-amino, trialkylammonium salt, (N)-carbamic dialkylamido, (N)-haloalkylamido, (N)-sulfonamido, (N)aryloxycarbamoyl, (N)-aralkyloxycarbamoyl hydroxy substituent on one or more of the alkyl alkylsulfonamido, (N)-haloalkylsulfonamido (N)-amido, (N)-alkylamido, -N-alkylamido, -N,Ntrialkylammonium (especially with a halide counterion), dialkylamino, (N)-alkoxycarbamoyl, (N)haloalkylsufonyl, amino, N-alkylamino, N,Ncarbonylalkyl amine, haloalkylthio, haloalkylsulfinyl, alkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxy-Among the preferred species which may

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butyloxycarbamoyl, (N)-methylsulfonamido, (N)N'-N-hexylamino, thiophene, -N'(CH,),CO,H I', -NCH,CH,CO,H, substituents can be advantageously present on the 6, 7, the 6,7,8-trimethoxy compounds. A variety of other included are the 6,7,8-trialkoxy compounds, for example disubstituted at the 7- and -8 positions. Also can be mono-substituted at the 6, 7 or 8 position, or pharmaceutically acceptable anion. The benzo ring is methylpyrrolidinium, and -(OCH,CH,),I, where A is a (N)-N'-dimethylpiperazinium I', (N)-tpoly(oxyalkylene) linkages, e.g., -(OCH;CH<sub>2</sub>),-N'R'R'R'N'A; quaternary ammonium salts linked to the ring via 8, and/or 9- positions of the benzo ring, including, where x is 2 to 10. Exemplary compounds are those set for example, guanidinyl, cycloalkyl, carbohydrate forth below in Table 1. (e.g., a 5 or 6 carbon monosaccharide), peptide, and

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Ph- 7-SCH2CH3

n-propyl

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IABLE 1
Alternative compounds #3 (Family F101.xxx.yyy) \*

Ng   11   12   12   13   13   13   13   13
<b>.</b>

R <sup>5</sup> (R <sup>x</sup> ) q	Ph- 7-methyl	Ph- 7-echyl	Ph- 7-iso-propyl	Ph- 7-terr-bucyl	Ph- 7-08	•	Ph- 7-0(iso-propyl)	Ph- 7-5CH3	Ph- 7-SOCH3	Ph- 7-50-74-1
R1=R2	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl g	n-propyl p	1-propyl p	n-propyl

#### \* General Notes

In the description of the substituents "(N)" indicates structure via the nitrogen atom. Similarly, 2-thiophene indicates a bond in the 2 position of the thiophene ring. A similar convention is used for other heterocyclic substituents.

Abbreviations and Definitions NH-CBZ is defined as -HNC(=0)OCH,Ph

7-NH2	7-инон	7-NHCH3	7-N (CH3) 2	7-N*(CH3)3, I"	7-NHC (=0) CH <sub>3</sub>	7-N (CH2CH3) 2	7-NMaCH2CO28	7-N*(Me) 2CH2CO2H, IT	7-(N)-morpholine	7-(N)-azetidine	7-(N)-N-methyleretidinium, I"	7-(N)-pyrrolidine	7-(N)-N-mathyl-pyrrolidinium, I'	7-(N)-N-methyl-morpholinium, I	7- (N) -N' -methylptperazine	7-(N)-N'-dimathylpiperatinium, I"	7-NB-CB2	7-NHC (0) C5H11	7-NHC (0) CH2Br	7-NH-C (NH) NH2	7-(2)-thiophene	8-methyl	8-ethyl	8-1so-propyl	8-tert-butyl	HO-8	8-осн3	8-0(iso-propyl)	8-SCH3	8-50CH3	8-S02CH3		8-NH2	в-инон		80	80	8-NHC (=0) CH <sub>3</sub>	8-N (CH2CH3) 2	8-NACH2CO2H	
놑	r L	Ę.	-dZ	-u	-ų	-ta	÷.	붑	-44	둩	ė	-h-	Ph-	Ë	Ph-	Ph-	-48	-ua	-Hª	Ph-	ę.	-qa	Ph-	-h	녚.	- L	-u	-E	-ua	- -	-ha	Ę.	- p-	-44	-ua	-ua	Ę	붑	-H	-H.	
n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	n-propyl	
12	2	14	15	16	11	18	19	70	21	22	23	24	25	26	27	28	53	30	33	32	33	34	35	36	33	38	33	Ç	7	42	43	44	45	4	<b>\$</b>	₩	6	20	51	22	

95 n-propyl Ph- 9-NH-CBZ	n-propyl	- K9		n-propy1 Ph- 9-(N)-N-methyl-pyrrolidinium, I		:	Depropy or	9	86 n-propyl Ph- 9-N*(Me)2CH2CO2H, I-	n-propyl Ph-	n-propyl ph-	n-propyl ph-	n-propyl Ph-	n-propyl ph-	n-propyl ph-	n-propyl ph-	Ph-	77 n-propyl Ph- 9-SCH2CH3	n-propyl ph-	75 n-propyl Ph- 9-socH <sub>3</sub>	n-propyl ph-	73 n-propyl Ph- 9-0(130-propyl)	,	Ph-	-u4	n-propyl ph-	n-propy1	67 n-propyl ph- d-mathyl	66 n-propy1 Ph- 8-{2}-thiophene	65 n-propyl Ph- 8-NH-C(NH)NH2	n-propyl Ph-	63 n-propyl Ph- 8-NHC(0)C5H11	62 n-propyl Ph- 8-NH-CBZ	61 n-propyl Ph- 8-(N)-N'-dimethylpiperazinium r-		8-(N)-N-methyl-morpholinium T	Ph-	Ph-	n-propyl Ph-	Ph-		53 n-propy1 Ph- 8-M*(Me),2CH2CO2H, I-
31	30	29	3 6	26	27	25	25	. 24	 2	22	3 *c	20 20	4 4			in t			111		ı,				, c	90	3 C	03		1	(TTT.aax. yyy)			103	102	101	100		99	98	97	96
n-butyl	n-buty1	n-bucy1	3	n-butvl	n-butyl	n-butyl	n-butyl			n-butyl				•			n-buty1													n-butyl	T-enx	10		n-propyl P	n-propyl P	n-propyl P	n-propyl P				n-propyl . P	n-propyl Pi
Ph- 7-NHC (0) CH2BE	£U- /-NUC(A)C2NII				Ph- 7-(N)-N'-methylpiperazine	Ph- 7-(N)-N-methyl-morpholinium, I	Ph- '7-(N)-N-methyl-pyrrolidinium, I'				7- (N) -marcholine		Ph- 7-NM-CH3CO3H			•	Ph- 7-N (CH1) 2		2h- 7-NHOH					571 7100H1		801 7:00H3			Ph- 7-ethyl	Ph- 7-methyl	× (× /9			Ph- 6-0CH3, /-0CH3, 8-0CH3		Ph- 7-SCH3, 8-OCH3	Ph- 7-ОСН3, 8-ОСН3		ph- 9-{2}-thiophene	Ph- 9-NH-C(NH)NH2	Ph- 9-NHC (0) CH2Bz	Ph- 9-NHC (O) C5H11

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		9-8CH3	9-502CH3	9-SCH2CH3	9-NH <sub>2</sub>	HOHN-6	9-NHCH <sub>3</sub>	9-N (CH3) 2	9-N+(CH3)3, I-	9-NHC (-0) CH3	9-N (CH2CH3) 2	9-NMeCH2CO2H	9-N* (Me) 2CH2CO2H, IT	9-(N)-morpholine	9-(N)-azetidine	9-(N)-N-methy)	9-(N)-pyrrolidine	9-(N)-N-methy	9-(N) -N-methy	9-(N)-N'-methylpiperazine	9-(N)-N'-dimet	283-HN-6	9-NAC (O) CHABE	9-NH-C (NH) NH	9-(2)-thiophene	•	7-0CH3, 8-0CH3	7-5сн3, 8-осн3		9-0cm3, 1-0cm3,		(R <sup>X</sup> )q		7-methy1	7-ethyl	7-iso-propyl	7-tert-butyl	7-0H	7-0CH	7-0(iso-propy))	7-574-
	á		i d	Ph.	Ph-	님	-H-	-4ª	-ua	-ea	-u-	-ta	-u&	-t2	-42 -42	-46	Ph-	4	-ua	-u	F 1			- da	- d		-t-	₽h-	-k &	į.		ξ.		-u	Ph-	-ua	-Hª	-48	Ė		2 4
	1	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-butyl	n-bury1	n-butyl	n-butyl	n-butyl	•	n-butyl	n-butyl	n-butyl	n-butvl		R1-R2		n-pentyl	n-pentyl	n-pentyl	n-pentyl	n-pentyl	n-pentyl	[2400-0	n-pencyt
WO 97/33882	ē	, ,	76	נג	78	7.9	80	18	82	83	8	82	98	81	88	68	90	16	35	93	g ;	Ç 4	2 6	. 86	5 6		100	101	102	202		₽ PdG	- 1			6	04	92	90	: 2	5 8
60 <b>%</b>																																Profile	(177.22	F101.003							
PCT/USy insk076	7-ин-С(ин) ин2	1- 7-(2)-thiophene					-						- 8-SCR2CH3	- 8-NH2				- 8-N+(CH3)3, I		- 8-N(CH2CH3)2						6- [N -pyrtolidine		-				_		B-(2)-thiophene		9-methyl	9-ethyl	9-1so-propyl			
PCT/USy/vot076	Ph- 7-NH-C(NH)NH2	Ph- 7-(2)-thiophene			ph 6-1-0		-		Ph- 8-0(1so-propyl)	Ph- 8-SCH3	Ph- 8-SOCH3	Ph- 8-502CH3	Ph- 8-SCR2CH3	Ph- 8-NH2	РЪ- 8-ИЮН	Ph- 8-NHCH3		Ph- 8-W*(CH3)3, I	Ph- 8-4XC (=0) CH <sub>3</sub>	Ph- 8-N (CH2CH3) 2					PA- 8-(N)-N-methylazetidinium, I-		Ph- 8-(N)-N-mathy Pytrotatatum, I	Ph- 8-(N)-N'-methylotherasion	Ph- 8-(N)-N'-dimethylpiperarinium. I	Ph- 8-NH-CBZ				Ph- 8-(2)-thiophene				Ph- 9-1so-propyl			
PCT/USy/AMOT6					- CA		4	Ph-	-ha	-H <b>4</b>	Ph-	Ph-	-ud	-ua	-ua	-ua	Ph-	- ua	-44	-ua	Ph-	-42 -42		ė a		-ua		-	Ph-	-ga	-u-	-ua		122		-H2	-H	Ph-			-46

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	51 n-pentyl Ph- 8-N(CH2CH1)2	n-pentyl Ph-	$n$ -pentyl $Ph$ - $\theta$ -N <sup>+</sup> (CH <sub>3</sub> ) <sub>3</sub> , I-		n-pentyl Ph- 8-NHCH3	n-pentyl Ph-	n-pentyl Ph-				n-pentyl Ph-	n-pentyl ph-	n-pentyl Ph-	36 n-pentyl Ph- 8-OH		36 h-pentyl Ph- 8-iso-propyl	- 48	34 n-pentyl Ph- 8-methyl		D-Depty   St.	n-pentyl ph	n-pencyl ph-	n-pentyl Ph-		Ph-	27 n-pentyl Ph- 7-(N)-N'-methylplperszine	26 n-pentyl Ph- 7-(N)-N-methyl-morpholinium, r-	25 n-pentyl Ph- 7-(N)-N-methyl-pyrrolidinium, r-	n-pentyl ph-	95-	Ph-	21 n-pentyl Ph- 7-(N)-morpholine	20 n-pentyl Ph- 7-W'(He), CH2CO2H, I-			17 n-pentyl Ph- 7-NHC (=0) CH <sub>3</sub>	16 n-pentyl Ph- 7-N <sup>+</sup> (CH <sub>3</sub> ) <sub>3</sub> , I	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	
	-	92	91 -	90 1		88	87 1	. 86	85 1	8 A A B	83 7	. 82 1	118	80 11	79 n	78 n	77 n	76 n	75 n	74 n	73 n	. 72 n	. 71 n		69 n	. B9	67 n		66 n	65 n	.64 n	63 n	. 62 n	61 n	60 n:	59 n-						53 n	52
n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-		n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl Ph-	n-pentyl . Ph-	n-pency1
9-(N)-N'-dimethylpiperazinium, I'	9-(N)-N'-methylpiperazine	9-(N)-N-methyl-morpholinium, I	9-(N)-N-methyl-pyrrolidinium, I-	9-(N)-pyrrolidine	9-(N)-N-methylazetidinium, I	9-(N)-azetidine	9-(N)-morpholine	9-N+ (Me) 2CH2CO2H, I-	9-NMeCH2CO2H	9-N (CH2CH3) 2	9~NHC (=0) CH3	9-N+(CH3)3, I	9-N (CH3) 2	9-NHCH3	9-NHOH	9-NH2	9-SCH2CH3	9-SO2CH3	9-SOCH3	9-SCH3 .	9-0(iso-propyl)	9-ОСН3	9-OH	9-ter-butyl	9-150-propyl	9-ethyl	9-methy1		8-(2)-thiophene	8-NH-C (NH) NH2	8-NHC (0) CH2Br	8-NHC(0)C5H11	8-NH-CBZ	8-(N)-N'-dimethylpiperazinium, I	8-(N)-N'-methylpiperazine	8-(N)-N-methyl-morpholinium, I	rrolidiniu	8-(N)-pyrrolidine	8-(N)-N-methylazetidinium, I	8-(N)-azetidine	8-(N)-morpholine	8-N*(Me)2CH2CO2H, I"	6-NM6CN2CU2n

PCT/US97/04076		n-hexyl . Ph-			n-nexy1		36 n-hexyl. sh- 8-1so-propyl		TAXOU-U		_	41 n-hexyl Ph- 6-5CH3	42 n-hexyl ph- 8-SOCH3	n-hexyl Ph-	n-hexvl		146	n-newy-	15401111	n-nexy.		50 n-bexyl Ph- 8-NHC(=0)CH3	n-hexyl Ph-	-hexyl	-hervi	140	n-hexy1	n-hexyl	n-hexyl	n-hexyl Pn-	44		20 1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-	n-hexyl	n-hexyl Ph-	n-heryl	-hexvl				p-hexvl ph- 9-mathyl		- No.	- Ag	-ud		n-hexyl rn-		Ä <sup>TT</sup>	<b>3</b>		
WO 97/33883											8-осиз																													-(N)-N-methylazetidinium, I"	ue u	7-(N)-N-methyl-pyrrolidinium, I	7-(N)-N-methyl-morpholinium, I-	piperazine	7-(N)-N'-dimethylpfperazinium, I						-	
		283-NH-C82	-qa		-e.	n-pantyl Ph- 9-(2)-thiophene		Physical Beauty, B-OCH3	7-SCH3,	8-SCH3	Ph- 6-0CH3, 7-0CH3,			Rleg R <sup>2</sup> (R <sup>2</sup> ) q		n-hexyl Ph- 7-methyl	n-hexyl Ph- 7-ethyl	n-hexyl Ph- 7-iso-propyl	n-bexyl Ph- 7-tert-butyl	n-hexyl Ph- 7-0H	n-hexyl Ph- 7-0CH3	- bp-	į.	ě		i di	-u-d	n-hexyl Ph- 7-NH2	n-hexyl Ph- 7-NHOH	n-hexyl Ph- 7-NHCH3	n-hexy1 Ph~ 7-N(CH3)2	- NA	á			-ua	•	n-hexyl Ph- 7-(N)-morpholine	n-hexyl Ph- 7-(N)-azetidine	n-hexyl Ph- 7-(N)-N-methyla	n-hexyl Ph- 7-{N}-pyrrolldine	n-hexyl Ph- 7-(N)-N-methyl-	n-hexyl Ph- 7-(N)-N-methyl-	n-hexyl Ph- 7-(N)-N'-mathylpiperatine	Ph-	1		n-heayl Ph- 7-NHC(0)CSH11		Ç	1.1	
	WO 97/53882			•		u 66			101	. 102 n				chq	(TIT. MAK. WAY)	F101.004 61 n	05	n 60	•0	050								12	13	77	135								22	23	24	25	26	23	28		£7 :	90				

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# Ph 9-SCH3  # Ph 9-SCH3  # Ph 9-SCH3  # Ph 9-SCH2CH3  # Ph 9-NHCH3  # P	7-0H	Ph-	iso-propyl	95	
# Ph	7-tert-butyl	<b>8</b> 4-	iso-propyl	04	•
# Ph 9-SCH3 #Y1 Ph 9-SCH3 #Y1 Ph 9-SCH3 #Y1 Ph 9-SCH2 #Y1 Ph 9-NOH #Y1 Ph 9-NH2 #Y1 Ph 9-NHCH3 #Y1 Ph 9-NH-BEHD1AzzELIGINIUM, IT #Y1 Ph 9-NH-MethylazzELIGINIUM, IT #Y1 Ph 9-NH-MethylazzELIGINIUM, IT #Y1 Ph 9-NH-MethylazzELIGINIUM, IT #Y1 Ph 9-NH-CH3 #Y1 Ph 9-NH-	7-iso-propyl	<b>P</b>	iso-propyl	8	
# Ph 9-SCH3  # Ph 9-SCH3  # Ph 9-SCH3  # Ph 9-SCH2  # Ph 9-NH2  # Ph 9-NHC  # Ph 9-NHC  # Ph 9-NHC  # Ph 9-NHC(H3)3, I*  # Ph 9-NHC(H3)2  # Ph 9-NHC(H3)2  # Ph 9-NHC(H3)3, I*  # Ph 9-NHC(H3)2  # Ph 9-NH-CH2CO2H, I*  # Ph 9-NH-Methylazetidinium, I*  # Ph 9-NH-CH3  # Ph 9-NH-CH3, 8-OCH3  # Ph 1-SCH3, 8-OCH3  # Ph 6-OCH3, 7-OCH3, 8-OCH3  # Ph 1-SCH3,	7-ethy1	Ph-	130-propy1	92	
# Ph 9-SCH3  # Ph 9-SCH3  # Ph 9-SCH3  # Ph 9-SCH2  # Ph 9-NH2  # Ph 9-NHC  # Ph 9-NH-CER2O2H, I  # Ph 9-NH-CER3O2H, I  # Ph 9-NH-CER2O2H, I  # Ph 9-NH-	7-methyl	Ph-	iso-propyl		F101.005
Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH2  Ph- 9-NHC  Ph- 9-NHC(H3)  Ph- 9-NHC(H3)  Ph- 9-NHC(H3)  Ph- 9-NHC(H2CH3)  Ph- 9-NHC(H2CH3)  Ph- 9-NH-MECH2CO2H  Ph- 9-(N)-M-methyl-pyrrolidine  Ph- 9-(N)-M-methyl-pyrrolidinum, I  Ph- 9-NH-CB2  Ph- 9-NHC(O)C5H11  Ph-	(R <sup>2</sup> ) q	n S	Rlag2	25 T	Profile (TIT. SEE.
Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-NH2  Ph- 9-NH2  Ph- 9-NHC  Ph- 9-NHC(CH3)3, I-  Ph- 9-NHC(CH3)3  Ph- 9-NHC(CH3)2  Ph- 9-NHC(CH3)2  Ph- 9-NHC(CH3)2  Ph- 9-NHC(CO2H)  Ph- 9-NHC(CO2H)  Ph- 9-NHC(CO2H)  Ph- 9-(N)-M-methylazetidinium, I-  Ph- 9-NH-CG2  Ph- 9-NH-CG3  Ph- 9-NH-CG3  Ph- 9-NH-CG3  Ph- 9-NH-CG43, 8-CCH3  Ph- 6-CCH3, 8-CCH3  Ph- 6-CCH3, 8-CCH3  Ph- 6-CCH3, 8-CCH3  Ph- 6-CCH3, 8-CCH3					
Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH2CH3  Ph- 9-NHC  Ph- 9-NHC(H3)2  Ph- 9-NHC(H3)2  Ph- 9-NHC(H3)2  Ph- 9-NHC(H2CH3)2  Ph- 9-NHC(H2CH3)2  Ph- 9-NHC(H2CH3)2  Ph- 9-NH-MECH2CO2H  Ph- 9-(N)-M-METHYLETEIDIAIUM, I-Ph- 9-(N)-M-METHYL-PYETOLIDIAIUM, I-Ph- 9-(N)-M-METHYL-PYETOLIDIAIUM, I-Ph- 9-NH-CO2CH3  Ph- 9-NHC(O)CH3Br  Ph- 7-SCH3, 8-OCH3  Ph- 7-SCH3, 8-SCH3	7-00	<b>P</b> 5-	n-hexvl	103	
Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH2  Ph- 9-NHC  Ph- 9-NHCH3  Ph- 9-NHCH3  Ph- 9-NHCH3  Ph- 9-NHCH2CH3)  Ph- 9-NHCH2CH3)  Ph- 9-NHCH2CH3)  Ph- 9-NHCH2CH3  Ph- 9-NHCH2CO2H, I-Ph- 9-(N)-Marchidine  Ph- 9-(N)-Marchidine  Ph- 9-(N)-Marchidine  Ph- 9-(N)-Marchyl-pyrrolidine  Ph- 9-(N)-Marchyl-pyrrolidine  Ph- 9-(N)-Marchyl-pyrrolidine  Ph- 9-(N)-Marchyl-pyrrolidine  Ph- 9-(N)-Marchyl-pyrrolidine  Ph- 9-(N)-Marchyl-pyrrolidinium, I-Ph- 9-(N)-Marchyl-pyrrolidinium, I-Ph- 9-(N)-Marchyl-pyrrolidinium, I-Ph- 9-(N)-Marchyl-pyrrolidinium, I-Ph- 9-(N)-Marchyl-pyrrolidinium, I-Ph- 9-(N)-Marchyl-pyrrolidinium, I-Ph- 9-NHC(O)CH3Br  Ph- 9-NHC(O)C		5-	n-hexyl	102	
Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH2  Ph- 9-NHC  Ph- 9-NHCH3  Ph- 9-NH-Pyrrolidine  Ph- 9-NH-Pyrrolidine  Ph- 9-NH-Pyrrolidine  Ph- 9-NH-Pyrrolidine  Ph- 9-NH-GOGBH  Ph- 9-NH-GOGBH  Ph- 9-NH-GOGBH  Ph- 9-NHCGOGBH  Ph- 9-NHCGGGBH  Ph- 9-NHCGGGBH  Ph- 9-NHCGGGBH  Ph- 9-NHCGGGBH  PH- 9-NHCGGGBH		<b>₽</b> ħ-	n-hexyl	101	
Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH3  Ph- 9-SCH2  Ph- 9-SCH2  Ph- 9-NHC  Ph- 9-NHC(H3)  Ph- 9-NHC(H3)  Ph- 9-NHC(H3)  Ph- 9-NHC(H3)  Ph- 9-NHC(H3)  Ph- 9-NHC(H3)  Ph- 9-NH-MECH2CO2H  Ph- 9-(N)-M-METHYLATELIGINIUM, I-PH- 9-(N)-M-METHYLATELIGINIUM, I-PH- 9-(N)-M-METHYLATELIGINIUM, I-PH- 9-(N)-M-METHYLATELIGINIUM, I-PH- 9-(N)-M-METHYLATELIGINIUM, I-PH- 9-(N)-M-METHYLATELIGINIUM, I-PH- 9-NH-COCHILI  Ph- 9-NH-CO		Ph-	n-hexyl	100	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2 Ph- 9-NHC Ph- 9-NHC(H3) Ph- 9-NH-CBZ Ph- 9-NHC(H3) Ph- 9	9-(2)-thlophene	₽h-	n-hexyl	99	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2GH3 Ph- 9-SCH2CH3 Ph- 9-SCH2CH3 Ph- 9-SCH2CH3 Ph- 9-NHCH Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NH-CH2CO2H Ph- 9-NH-mathylazetidinium, I-Ph- 9-NH-mathyl-pyrolidine Ph- 9-NH-mathyl-pyrolidinium, I-Ph- 9-NH-C82 Ph- 9-NH-C82 Ph- 9-NHC(0)C5H1	9-NH-C (NH) NH2	Ph-	n-hexyl	98	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2GH3 Ph- 9-SCH2CH3 Ph- 9-SCH2CH3 Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NH-CH2CO2H Ph- 9-NH-morpholine Ph- 9-(N)-morpholine Ph- 9-(N)-morpholinie Ph- 9-(N)-M-morpholinie Ph- 9-(N)-M-morpholinie Ph- 9-(N)-N-morpholinie Ph- 9-NH-CB2	9-NKC (0) CH2Br	Ph-	n-bexyl	97	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2CH3 Ph- 9-SCH2CH3 Ph- 9-SCH2CH3 Ph- 9-NOH Ph- 9-NHCH3 Ph- 9-NHC(H3)3, I* Ph- 9-NHC(H3)2 Ph- 9-NHC(H2CH3)2 Ph- 9-NHC(H2CH3)2 Ph- 9-NH-CH2CO2H Ph- 9-NH-morpholine Ph- 9-(N)-morpholine Ph- 9-(N)-morpholinium, I* Ph- 9-(N)-M-morpholinium, I* Ph- 9-(	9-NHC (O) C5H11	-4g	n-hexyl	96	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2 Ph- 9-SCH2 Ph- 9-SCH2 Ph- 9-NHC Ph- 9-NHC(H3) 3, I* Ph- 9-NHC(H3) 3, I* Ph- 9-NHC(H2CH3) 2 Ph- 9-NHC(H2CH3) 2 Ph- 9-NH-methylazetidinium, I* Ph- 9-(N)-methylazetidinium, I* Ph- 9-(N)-Methylazetidinium, I* Ph- 9-(N)-Methylazetinium, I* Ph- 9-(N)-Methylazetinium, I* Ph- 9-(N)-N-methylazetinium, I* Ph- 9-(N)-N-methylazetinium, I* Ph- 9-(N)-N'-methylazetinium, I* Ph- 9-(N)-N'-dimethylazetinium, I* Ph- 9-(N)-N'-dimet		-48	n-hexyl	95	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2 Ph- 9-SCH2CH3 Ph- 9-NHCH Ph- 9-NHCH3 Ph- 9-NHCH3 Ph- 9-NHCH2CH3) 3, I' Ph- 9-NHCH2CH3) 2 Ph- 9-NHCH2CH3) 2 Ph- 9-NHCH2CH3 2 Ph- 9-NHCH2CH3 1 Ph- 9-NH-METHYLAZETIGLINIM, I' Ph- 9-(N)-M-methyl-pyzzolidinium, I' Ph- 9-(N)-M-methyl-pyzzolidinium, Ph- 9-(N)-M-methyl-pyzzolidinium, Ph- 9-(N)-M-methyl-pyzzolidinium, Ph- 9-(N)-M-methyl-mezpholinium, Ph- 9-(N)-N-methyl-mezpholinium, Ph- 9-(N)-N-methyl-pyzzolidinium, Ph- 9-(N)-N-methyl-mezpholinium, Ph- 9-(N)-N-methyl-pipezzine	9-(N)-N'-dimethylpiperazinium, I	<b>9</b> 7-	n-hexyl	93	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2 Ph- 9-SCH2 Ph- 9-SCH2CH3 Ph- 9-NCCH3 Ph- 9-NCCH3 Ph- 9-NCCH3 Ph- 9-NCCH3 Ph- 9-NCCH3 Ph- 9-NCCH3 Ph- 9-NCCH2CH3 Ph- 9-NCCH2CH3 Ph- 9-NCCH2CH3 Ph- 9-NCCH2CH3 Ph- 9-NCCH2CH3 Ph- 9-NCCH2CO2H Ph- 9-NCCH3CO2H P		Ph-	n-hexyl	93	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2 Ph- 9-SCH2 Ph- 9-NH2 Ph- 9-NHCH3 Ph- 9-NHC(H3) 2 Ph- 9-NH(CH3) 3, I' Ph- 9-NH(CH3) 3, I' Ph- 9-NH(CH2CH3) 2 Ph- 9-NHCH2CO2H Ph- 9-N'(Ma) 2CH2CO2H, I' Ph- 9-(N)-Morpholine Ph- 9-(N)-Pyrrolidine Ph- 9-(N)-Pyrrolidine Ph- 9-(N)-Pyrrolidine Ph- 9-(N)-Pyrrolidine Ph- 9-(N)-Pyrrolidine		Ph-	n-hexyl	92	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2 Ph- 9-SCH2 Ph- 9-SCH2 Ph- 9-NH2 Ph- 9-NH2 Ph- 9-NHC Ph- 9-NHC(H3) 3, I' Ph- 9-NHC(H3) 2 Ph- 9-NHC(H3) 3 Ph- 9		P 7	n-hexyl	91	
Ph- 9-SCH3 Ph- 9-SCH3 Ph- 9-SCH2 Ph- 9-SCH2 Ph- 9-SCH2 Ph- 9-NHC Ph- 9-NHC(H3)2 Ph- 9-NHC(H3)3 P		Ph-	n-hexyl	90	
Ph- 9-5CH3 Ph- 9-5CH2 Ph- 9-5CH2 Ph- 9-502CH3 Ph- 9-502CH3 Ph- 9-802CH3		Ph-	n-hexyl	89	
Ph- 9-5CH3 Ph- 9-5CH2 Ph- 9-5CH2 Ph- 9-5CH2CH3 Ph- 9-8CP2CH3 Ph- 9-NHC Ph- 9-NHC(H3)2 Ph- 9-NHC(H3)2 Ph- 9-NHC(H3)2 Ph- 9-NHC(H2CH3)2 Ph- 9-NHC(H2CH3)2 Ph- 9-NHC(H2CH3)2 Ph- 9-NHC(H2CO2H Ph- 9-N'(NH)2CH2CO2H Ph- 9-N'(NH)	9-(N)-azetidine	Ph-	n-hexyl	88	
Ph- 9-5CH3 Ph- 9-5CH2 Ph- 9-5CH2 Ph- 9-5CH2CH3 Ph- 9-802CH3 Ph- 9-NHC Ph- 9-NHCH3 Ph- 9-NHC(H3)2 Ph- 9-NHC(=0)CH3 Ph- 9-NHC(=0)CH3 Ph- 9-NM-6CH2CO2H Ph- 9-NM-6CH2CO2H Ph- 9-NM-6CH2CO2H	9-(N)-morpholine	-u4	n-hexyl	87	
בר ק ה ה ק ק ק ה ה ה ק ק ק		Ph-	n-hexyl	96	
בין המק המק המק המק המק המק המק המק המק המק	9-NMeCH2CO2H	Ph-	n-hexyl	85	
בין המק המק המק המק המק המק המק המק המק המק	9-N (CH2CH3) 2	Ph-	n-hexyl	84	
בים המק המק המק המק המק המק המק המק המק המק	9-NHC (=0) CH3	₽h-	n-hexyl	83	
בין המק המק המק המק המק המק המק המק המק המק		Ph-	n-hexyl	82	
7 P P P P P P P P P P P P P P P P P P P	9-N (CH3) 2	Ph-	n-hexyl	18	
	9-NHCH3	Ph-	n-hexyl	80	
2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	9-инон	Ph-	n-hexyl	79	
יים לי קיים מים מים מים מים מים מים מים	9-NH2	Ph-	n-hexyl	78	
P 20 20 20 20 20 20 20 20 20 20 20 20 20	9-SCH2CH3	Ph-	n-hexyl	77	
	9-S02CH3	Ph-	n-hexyl	76	
	9-SOCH3	Ph-	n-hexyl	75	
	9-SCH3	Ph-	n-hexyl .	74	
3	9-0(iso-propyl)	Ph-	n-hexyl	73	

50	49	48	47	. 46	45	**	43	42	41	40	99	38	37	36	35		33	32	te	30	. 29	. 28	27	. 26	25	24	. 23	22	21	20	19	18	17	16	15	14	13	12	11	10	
iso-propyl	iso-propyl	1so-propyl	iso-propyl	iso-propyl	iso-propyl	190-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propy1	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl :	iso-propyl	iso-propyl 1	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl	iso-propyl . I	iso-propyl I
P	-48	<b>P</b> 5-	-4 <b>4</b>	27-	<b>2</b> h-	9	Ph-	-44	2	Ph	<b>P</b> h-	25	Ph-	Ph-	10	Pa-	24	-4g	Ph-		24	2	Ph-	?	. d	<b>P</b>	- 4	<b>Ph</b>	Ph-	Ph-	P	7	Ph-	Ph-	<b>Ph-</b>	-48	-44	P	Ph-	P -	Ph-
8-NHC (=0) CH3	8-N+(CH3)3, I	8-N (CR3) 2	8-NHCH3	8-NHOH	8-NH2	B-SCH2CH3	8-502СН3	.B-20CH3	8-SCH3	8-0(iso-propyl)	8-0CH3	8-OH	8-tert-butyl	8-iso-propyl	8-ethyl	0-methyl	7-(2)-thiophene	7-NH-C (NH) NH2	7-NHC (0) CH2BE	7-NHC (0) C5H11	7-NH-CBZ	7-tm -N'-dimethylpiperazinium, I'	7-(N)-N'-methylpiperazine	7-(N)-N-methyl-morpholinium, I	7-{N}-N-methyl-pyrrolidinium, I	7-(N)-pyrrolidine	7-{N}-N-methylazetidinium, I	7-(N)-azetidine	7-(N)-morpholine	7-N+(Me)2CH2CO2H, IT	7-NMeCH2CO2H	7-N(CH2CH3)2	7-NHC (=0) CH3	7-N+(CH3)3, I	7-N(CH3)2	7-NHCH3	7-NHOH	7-NH2	7-SCH2CH3	7-S02CH3 ·	7-SOCH3

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iso-propyl
iso-propyl
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2 2 2 2 2 2 2

7-0(iso-propyl) 7-SCH3 7-OCH<sub>3</sub>

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15	1so-propyl	ę.	8-N (CH2CH3) 2		(Marianes)	j.	ä	The state of the s
\$2	. 130-propyl	-q2	8-NMeCH2CO2H	ה ה ה			i 4	o-no-co-
53	1so-propyl	-ų	8-N'(Me),CH2CO2H, I"	96		ropy]	Ė	9-NKC(0) C4H11
54	iso-propyl	Ph-	8-(N)-morpholine	97		ropyl	-44	9-NHC (O) CH28r
80 80	iso-propyl	-d	8-(N)-aretidine	85		ropyl	-12	9-NH-C (NH) NH2
	1so-propyl	-ya	8-(N)-N-methylezetidinium, I-			copyl	- d	9-(2)-thiophene
57	iso-propyl .	Ę	8-(N)-pyrrolidine	•			:	
86	130-propyl	-42	8-(N)-N-methyl-pyrrolidinium, I	100	1 iso-propyl	ropyl	-u-	7-осиз, 8-осиз
65	iso-propyl	-48	8-(N)-N-methyl-morpholinium T-			ronvi		7-SCH1. 8-0CH1
9	iso-propyl	-4 <b>4</b>	8-(N)-N'-methylpiperatine			- 600	: 6	7=5CH3 - B=SCH3
19	iso-propyl	Ph-	8-(N)-N'-dimethylotoerazinim r-	103		1600	: <del> </del>	6-0CH3, 7-0CH3, 6-0CH3
62	iso-propyl	-t4	8-NH-CB2					
63	iso-propyl	-ea	8-NHC (0) C5H11					
, 64	iso-propyl	Ph-	8-NHC (0) CH2Br		d# Rleg2		z,	(R*) q
65	iso-propyl	-44 -44	8-NH-C (NH) NH2				١	
99	1so-propyl	Ph-	8-(2)-thiophene	F101.006 01		ucyl		/-metny1
				70		ucy.		l-deny.
67	iso-propyl	-ųa	9-methyl	03		utyl	٠ ا	7-iso-propyl
89	1so-propyl	Ph-	9-ethyl	20		utyi	ב ב	/-tert-puty.
69	1so-propyl	-4a	9-Lao-propyl	92		utyl	i C	7-0#
0,	iso-propyl	-ua	9-tert-butyl	90	•	utyl	, E	7-0083
11	iso-propyl	-q&	9-0K	. 07	•	utyl	Ë	7-0(iso-propyl)
27	1so-propyl	-u	9-осн <sub>3</sub>			utyl	- E	7-SCH3
73	1so-propyl	-H2	9-0(iso-propyl)	60	iso-butyl	utyl	-ua	7-50CH3
7.4	1so-propyl	-u a	9-SCH <sub>3</sub>	10	1so-butyl	utyl	ę.	7-S02CH3
75	iso-propyl	Ę.	9-SOCH <sub>3</sub>	<b>a</b>		utyl	-u &	7-SCH2CH3
96	iso-propyl	-ta	9-502CH3	12	1so-butyl	utyl	-u	7-NH2
77	iso-propyl	÷.	9-SCH2CH3	13	1 iso-butyl	utyl	-H-	7-NHOH
78	iso-propyl	-4 <u>4</u>	- CHN-6	14	1 tso-buty1	utyl	- E	7-NHCH3
79	iso-propyl	- - - -	HOWN-6	15	i iso-butyl	utyl	占	7-N(CH3)2
8.	iso-propyl	-h-	9-NHCH1	91	i iso-butyl	utyl	-ua	7-N+(CH3)3, I
81	iso-propyl	-H	9-N (CH <sub>3</sub> ) <sub>2</sub>	7.1	1 iso-butyl	outyl	Ph-	7-NHC (=0) CH3
82	iso-propyl	-ua	9-N <sup>+</sup> (CH <sub>3</sub> ) <sub>3</sub> , I <sup>-</sup>	18	i iso-butyl	outyl	-ua	7-N (CH2CH3) 2
83	1so-propyl	-48	- CC - C - C - C - C - C - C - C - C -	19	1 iso-butyl	outyl	Ph-	7-NM6CH2CO2H
84	1so-propyl	-ua	C::20 X-6	20	) iso-butyl	outyl	-ua	7-N* (Me) 2CH2CO2H, I
88	1so-propyl	Ę.	7 COUCHUMN-6	21		iso-butyl	₽ <b>₽</b>	7-(N)-morpholine
98	1so-propy1	Ę		22		iso-butyl	-q	7-(N)-azetidine
87	1so-oro	. 4	0 /11/	23		iso-butyl	Ph-	7-(N)-N-mathylazetidinium, I
88	tao-propri	1 1		24		Iso-butyl	-44	7-(N)-pyrrolidine
68	1ao-propyl	1 6		25		so-butyl	-hg	7-(N)-N-methyl-pyrrolidinium, 'I'
90	1so-propyl	: :	0-(N) -N-metnylazetidinium, I	7	26 130-k	1so-butyl	F	7-(N)-N-mathyl-morpholinium, I
16	140-11-01	1	3-(N)-pyrrolidine	7.2		iso-butvl	d d	7-(N)-N'-methylpiperatine
3 2	fac-propyl		9-(N)-N-methyl-pyrrolidinium, I	. 2		1so-butyl	-H-	7-(N)-N'-dimethylpiperazinium, I
	1so-propyr					1so-butyl	Ph-	7-NH-CB2
}	* 1.40.4.4. 00.4	1 12 25 26	y-(N)-N'-mathylpiperatine	1		•		

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iso-butyl	iso-butyl	150-buty1	TADO-DUE Y	120 5447	140-5-1	TANG- PARY T	100-00-01	iso-but vi	iso-butyl	iso-butyl	iso-butyl	1so-buty1	iso-butyl	Tan-puty1	iso-butyl	iso-butyl	iso-butyl	TAO-DUCAT	150-buty1	and bury	iso-butul	f en-hut wi	iso-but vi	iso-butvl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	1so-butyl	150-butyl	iso-butyl .	1so-butyl	iso-butyl	iso-butyl		iso-butyl	iso-butyl	1so-butyl .	iso-butyl
Ph-	Ph-	<b>1</b> 9	52	¥21-	;	3	: :	2	P	Ph-	Ph-	2	, e	Ph-	Ph-	Ph-	Ph-	-44	Ph-	- Ya-	? ?	,	7 :	9	P)	Ph-	<b>P</b> 2	<b>P</b>	Ph-	<b>P</b> 7-	<b>P</b> h-	Ph-	Ph-	<b>Ph-</b>	Ph-	-44	Ph-	Ph-	-4¢	<b>P</b> h-		뫍	55-	<b>P</b>	Ph-
9-0H	9-cert-butyl	9-iso-propyl	9-ethyl	y-methy1		8-(2)-thiophene	0-Nn-C(NH) NR2		B-NHC (O) CH2BT	8-NHC(0)C5H11	8-NH-CB2	8-(N)-N'-dimethylpiperazinium, I'	8-(N)-N'-methylpiperazine	8-(N)-N-methyl-morpholinium, I-	8-(N)-N-methyl-pyrrolidinium, I-	8-(N)-pyrrolidine	8~(N)-N-methylazetidinium, I	8-(N)-exetidine	8- (N) -morpholine	8-N"(Me) 2CH2CO2H, I"	a-NMeCH2CO2H	6-N(Cn2Cn3)2	9-W(C)-07-Ca3		BINIT COLOR	8-항(CH1) 2	8-NHCH3	8-NHOH	8-NH2	8-SCH2CH3	8-SO2СИ3	8-SOCH3	8-SCH3	8-0(iso-propyl)	8-ОСН3	HO-8	8-tert-buty1	8-iso-propy1	0-ethyl	6-methyl		7-(2)-thiophene	7-NH-C (NH) NH2	7-NHC (0) CH2Br	7-NHC (0) C5H11
								(FTT . xxx.	Prafix																																				
07	0	3	2 2	2	03	2 1	2	1	2			103	102	101	100		99	98	97	96	95	93	93	92	91	90	89	88	87		. 5		2 2	3	82	2	90	79	78	77	76	75	74	73	72
iso-pentyl	150-penty1	Tao-bency T	tenponty.		iso-pentyl	iso-pentyl	iso-pentvl	,	n1=n2			1so-butyl	iso-butyl	iso-butyl	iso-butyl		iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	150-DUEY1	150-00571	rao-pucyr	150-bucy1		iso-butvl	150-butyl	1so-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl	iso-butyl .	iso-butyl
Ph-	Pn-	;	g :	9 :	2 :	9 :	P	,	5			<b>Ph-</b>	Ph-	<b>9</b> 5-	Ph-		P 7	<b>2</b> 7	<b>9</b> 7	₽ħ-	Ph-	50.	-44	20	Ph-	Ph-	Ph-	P)-	P	Pn-	1 10	70	7 7	;	8	9	Ph-	Ph-	7	Ph-	P.7	P)-	Ph-	<b>Ph</b> -	-44
7-0(iso-propyl)	1-OCH3	1-01		Jerost - hity	7-iso-propyl	7-achyl	7-methvl	7	(EX) 7				7-SCH3, 8-SCH3	7-SCH3, 8-OCH3	7-осн3, 8-осн3		9-(2)-thiophene	9-NH-C (NH) NH2	9-NKC (0) CH2Bz	9-NHC (O) C5H11	9-NH-CBZ	9-(N)-N'-dimethylpiperazinium, I	9-(N)-N'-methylpiperazine	9-(N)-N-methyl-morpholinium, I	9~(N)-N-methyl-pyrrolidinium, I-	9-(N)-pyrrolidine	9-(N)-N-methylazetidinium, I"	9-(N)-azetidine	9- (N) -morpholine	9-N" (Me) 2CH2CO2H, I"		9-N (CM2CM3) Z	9-NAC (=0) CH3	3-10 (ch3) 3, +	PLN+COPY TO	9-N (CH <sub>3</sub> ) 2	9-NHCH3	9-инон	9-NH2	9-SCH2CH3	9-SO2CH3	9-SOCH3	9-SCH3	9-0(iso-propyl)	9-осн3

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Trefix Cpd# [FIT.sex. YYY] -101.008 01 02 03		P 7 7 75	(R <sup>±</sup> ) q 7-methyl
		Ph-	7-methyl
	CH <sub>2</sub> C (=0) C <sub>2</sub> H <sub>3</sub>	Ph-	
0 0	CH-C (40) C-B-		7-echyl
0.4	Guza to taling	Ph-	7-iso-propyl
	CH2C (-0) C2H3	Ph-	7-text-butyl
05	CH2C (-0) C2H3	Ph-	7-04.
90	CH2C (-0) C2H3	Ph-	7-0CH <sub>3</sub>
07	CH2C (-0) C2H5	8 h-	7-0(iso-propyl)
80	CH2C (=0) C2H5	Ph-	7-SCH3
09	. CK2C (-0) C2H2	74	7-SOCH3
10	CH2C (=0) C2H5	-44	7-so <sub>2</sub> ch <sub>3</sub>
ıı	CH2C (-0) C2H5	<b>Ph-</b>	7-SCH2CH3
12	CH2C (=0) C2H5	₽ħ-	7-NH2
13	CH2C (=0) C2H5	Ph-	7-NHOH
14	CH2C (=0) C2H5	Ph-	7-NHCH3
15	CH2C (=0) C2H5	<b>5</b> 4-	7-N (CH3) 2
16	CH2C (-0) C2H5	₽ħ.	7-N+(CH3)3, I
17	CK2C (=0) C2H3	Ph-	7-NHC (-0) CH3
18	CH2C (=0) C2H5	Ph-	7-N (CH2CH3) 2
19	CH2C (=0) C2H5	₽. -	7-NMeCH2CO2H
20	CH <sub>2</sub> C (=0) C <sub>2</sub> H <sub>5</sub>	-44	7-N+(Me) 2CH2CO2H, I"
21	CH2C (-0) C2H5	Ph-	7-(N)-morpholine
22	CH2C (=0) C2H3	2h-	7-(N)-azetidine
23	CH2C (=0) C2H5	Ph-	7-(N)-N-methylazetidinium, I"
24	CH2C (=0) C2H5	Ph-	7-(N)-pyrrolidine
25	CH2C (=0) C2H5	Ph-	7-(N)-N-methyl-pyrrolidinium, I
26	CH2C (=0) C2H5	Pb-	7-(N)-N-methyl-morpholinium, I-
27	CH2C (=0) C2H5	Ph-	
28	CH2C (=0) C2H5	₽ħ-	7-(N)-N'-dimethylpiperazinium, I"

103	102	101	100	99	98	97	96	95	93	¥
iso-pentyl	iso-pentyl	iso-pentyl	iso-pentyl	1so-pentyl	iso-pentyl	iso-pentyl	iso-pentyl	iso-pentyl	iso-pentyl .	130-pentyl
-44	Ph-	<b>P</b> h-	Ph-	. *g	Ph-	Ph-	<b>₽</b> h-	Ph-	Ph-	<b>Ph-</b>
6-0CH <sub>3</sub> ,	7-SCH <sub>3</sub> ,	7-SCH3, 8-ОСН3	7-0CH <sub>3</sub> ,	9- (2) -t	9-NH-C (NH) NH2	9-NHC (0) CH2Br	9-NHC (O) C5H11	9-NH-C8Z	9- (N) -k	9- (N) -
6-осиз, 7-осиз, в-осиз	7-SCH3, 8-SCH3	8-0CH3	7-осн <sub>3</sub> , 8-осн <sub>3</sub>	9-(2)-thiophene	NH) NH2	CH2Br	)C5H11	2	/ -dimeth	"-methyl
в-осн3									9-(N)-N'-dimethylpiperazinium, I	9- (N) -N' -methylpiperazine
									ч	

69	68	67	66	65	64	63	62	13	60	59	58	57	56	55	54	53	52	51	50	49	<b>8</b>	47	46	45	44	43	12	4	ô	39	<b>8</b>	37	36	35	34	33	<b>3</b> 2	31	30	29
CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH <sub>2</sub> C (=0) C <sub>2</sub> H <sub>5</sub>	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H3	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H3	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H3	CH2C (=0) C2H5	CH2C (=0) C2H3	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H3	CH2C (-0) C2H3	CH2C (=0) C2H5	CH2C (=0) C2H5	CH2C (=0) C2H3	CH2C (=0) C2H5 .	CH2C (=0) C2H5						
₽h-	<b>P</b> A-	Ph-	Ph-	5 V-	Ph-	-44	Ph-	Ph-	Ph-	<del>ខ្</del> គក-	₽h-	Ph-	Ph-	Ph-	Ph-	Ph-	Ph-	5 P.	Ph-	Ph-	P 7	Ph.	Ph-	Ph-	Ph-	<b>Ph-</b>	Ph-	<b>Ph-</b>	Ph-	Ph-	Ph-	Ph-	₽h~	Ph-		8 p	Ph-	Ph-	Ph-	Ph-
9-iso-propyl	9-ethyl	9-methyl	8-(2)-thiophene	8-NH-C (NH) NH2	8-NHC (0) CH2Br	8-NHC (O) C5H11	8-NH-CBZ	8-(N)-N'-dimethylpiperaziniu	8-(N)-N'-methylpiperazine	8-(N)-N-methyl-morpholinium,	8-(N)-N-methyl-pyzzolidinium	8-(N)-pyrrolidine	8-(N)-N-methylaretidinium, I	8-(N)-azetidine	8-{N}-morpholine	8-N*(Me)2CH2CO2H, IT	8-NMeCH2CO2H	8-N (CH2CH3) 2	8-NHC (-0) CH3	8-N+(CH3)3, IT	8-N (CH3) 2	8-NKCH3	8-МКОН	8-NH2	8-SCH2CH3	8-SO2CH3	8-SOCH3	8-SCH3	8-0(iso-propyl)	8-осн3	8-ОН	8-tert-butyl	8-iso-propyl	8-ethyl	8-methy1	7-(2)-thiophene	7-NH-C (NH) NH2	7-NHC (0) CH2Br	7-NHC (0) C5H11	7-NH-CBZ

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۶	: 0.01,010			•	•		
2 1	Cu2C1-01-243	Ę	- 9-tert-butyl	ž	20,00	å	10°
7.1	CH2C (=0) C2H3	남	HO-6 -	S	Cn20C2n3		101.
72	CH2C (=0) C2H3	-44	9-DCH2	90	CH2OC2HS .	-u.	7-0CH3
	CH2C (=0) C3H3	į		01	CH20C2HS	-H2	7-0(iso-propyl)
74	CH,C (=0) C,H;	. á		80	CH20C2HS	Ph-	7-SCH <sub>3</sub>
. 75	CR3C (=0) C.H.			69	CH2OC2H5	-ha	7-ѕосн3
9,6	CHOCADO			10	CH20C2H5	-ua	7-S02CH3
	CHO (=0) C2H3	ė ;		ផ	CH,0C,Hs	Ph-	7-SCH2CH3
	Eu2010-102m2	Ę.		12	CHOCAR	-da	7-NH2
	Cu-C (=0) C2H3	<u>-</u>		1 2	CHOCORS	- 4a	HOHN-L
	C4.0(-0) C2HS	-ua		41	CHOCOHO	-48	7-NHCH3
3 6	CA2C (=0) C2H3	-E			5H-0CH-0	<u> </u>	( ext) x=0
1 (	CH2C (=0) C2H3	Ę	9-N(CH3) <sub>2</sub>	? ;	6700,110	i	7,000
82	CH2C (=0) C2H3	-H2		31	CH2OC2HS	1 2	7-N (CH3) S. I
. 83	CH2C (=0) C2H3	ď		11	CH <sub>2</sub> OC <sub>2</sub> H <sub>5</sub>	<b>-</b>	7-NHC (=0) CH <sub>3</sub>
9.	CH2C (=0) C2H5	å		81	CH2OC2H5	- - -	7-N(CH2CH3)2
88	CH2C (=0) C3H4			19	CH20C2H5	-u	7-NMeCH2CO2H
98	CH,C(=0)C,H,			50	CH20C2H5	-44 -44	7-N' (Me) 2CH2CO2H, I"
87	: 0:0-/ U-NU	- C	9~N"(Me)2CH2CO2H, I"	21	CH10C1Hs	- dd	7-(N)-morpholine
	CH2C   -01 C2H3	둢	9-(N) -morpholine	: :		į	7-(N)-azetidine
8 3	CH2C (-0) C2H3	Ę	9-(R)-azetidine	3 :	cusocsus	: :	The state of the s
68.	CH2C (=0) C2H5	-u-d		<b>E</b> Z	CH2OC2HS		-(N)-N-mernyrazeriorum, i
06	CH2C (=0) C2H5	- d	9-(N)-purry) (Alex	24	CH2OC2H3	녙	7-(N)-pyrrolidine
	CH2C (=0) C2H4	2		. 25	CH2OC2H5	- - -	7-(N)-N-methyl-pyrrolidinium, I'
. 92	CH2C (-0) C2H2	, E	o-mi w -menachyr-pyrrolidinium, r	36	CH2OC2H5	붑	7-(N)-N-mathyl-morpholinium, I
66	CHOC (=0) C.H.	á	3"(N) -N-methyl-morpholinium, I".	27	CH2OC2H5	Ph-	7- (N) -N' -methylpiperazine
93	CK3C(-0)C3K3		3-(n)-N-methylperezine	28	CH2OC2H5	-hg	7-(N)-N'-dimethylpiperazinium, I'
56	CH-C (O-C) C-H-C		9-(N)-N'-dimethylpiperazinium, I-	. 29	CH20C2H5	-HZ	7-NH-CBZ
96	5 10 (0 10 m)		7-NH-CB2	30	CH2OC2H5	-t2	7-NHC (0) C5H11
	C"2-1-01-243	- G	9-NHC(0) C5H11	=	CHOCAR	-hg	7-NHC (0) CH2BE
	CH2C (=0) C2H5	Ę	9-NHC (O) CH2BF		*H*10*H1	4	7-NH-CHNICHOL
	CH2C (=0) C2H3	ż	9-NH-C (NH) NH2		6.7		
<b>9</b>	CH2C (=0) C2H3	Ph-	9-(2)-thiophene	E E	CH2OC2HS		יין בין יינודס ליינוים
100	CH-C (=0) C-R-	á		34	CH2OC2H5	i.	8-methyl
101	CH-C (*0) C-R-		/-OCH3, B-OCH3	35	CH20C2H5	-4 6	8-ethyl
102	CHar (mr) ray.		/-scha, B-ocha	36	CH20C2Ns	- H G	8-iso-propyl
103	CH-C (=0) C-U-	5 6	ASCH3, 8-SCH3	37	CH20C2H5	-u	8-tert-butyl
	(21.2/10)			38	CH20C2H3	-44 -44	H-O-B
				39	CH20C2H3	-Ha	B-0CH3
	R1=R2	2	- Feb	9	CH,OC,Hs	Ph-	8-0(iso-propyl)
(au				Ţ	CH20C2H5	Ph-	8-SCH3
10 600 . TOT	CH2OC2H5	-48	7-methyl	42	CH20C2H3	4	8-soch3
20 3	CH <sub>2</sub> OC <sub>2</sub> H <sub>5</sub>	-h	7-ethyl	\$	CH2OC2H3	, E	8-502CH3
6 ;	CH2OC2H3	å	7-iso-propyl	7	CH20C2H5	- ud	8-SCH2CH3
•	CH2OC2H3	Ph-	7-tert-butyl	45	CH2OC2H5	-H.	8-NH2

	Ph- 8-0CH3		Ph- 8-SCH <sub>3</sub>	h- 8-sock3		Ph- 8-SCH2CH3	Ph- 8-NH2	Ph- 8-NHOH	
	CH2OC2HS P		CH2OC285 P		CH2OC2H5 P	CH20C2H5 P	CH2OC2H5 P	CH2OC2H5 F	
89	39	9	ij	42	<b>\$</b>	7	45	46	

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87	86	85	0	83	82	18	8	79	78	77	76	75	74	73	72	7.	70	69	68	67		6	65	64	8	62	19	60	59	<b>8</b>	57	56	55	54	53	52	51	50	49	8	\$
CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH <sub>2</sub> OC <sub>2</sub> H <sub>3</sub>	CH2OC2H3	CH2OC2H3	CH2OC2H5	CH2OC2H5	•	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H3	CH <sub>2</sub> OC <sub>2</sub> H <sub>5</sub>	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2R3	CH2OC2H5	CH2OC2H5	CH2OC2H3	CH2OC2H5	CH <sub>2</sub> OC <sub>2</sub> H <sub>5</sub>	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2HS .	CH2OC2H5
Ph-	Ph-	<b>Ph-</b>	Ph-	<b>P</b> 7	Ph-	₽,	<b>9</b>	-44	P -	P -	Ph-	Ph-	<b>P</b>	-44	<b>9</b>	Ph-	Ph-	-44 -44	Ph-	Ph-		Ph-	₽h-	Ph-	Ph-	<b>P</b>	Ph-	8h-	2	-44	-44	Ph-	Ph-	Ph-	<b>P</b> A-	Ph-	Ph-	<b>P</b> 5	<b>P</b> 7	<b>P</b>	2
9-(N)-morpholine	9-N*(Me)2CH2CO2H, I"	9-NMeCH2CO2H	9-N (CH2CH3) 2	9-NHC (=0) CH3	9-N+(CH3)3, I-	9-N(CH <sub>3</sub> ) <sub>2</sub>	9-NECH3	9-NHOH	9-NH2	9-SCH2CH3	9-\$02CH3	9-SOCH3	9-SCH3	9-0(iso-propyl)	9-OCH3	9-0H	9-tert-butyl	9-iso-propyl	9-ethyl	9-methy1		8-(2)-thiophene	8-NH-C (NH) NH2	8-NHC(0)CH2B=	8-NHC(0) C5H11		8-(N)-N'-dimethylpiperazinium, I"	8-{N}-N'-mathylpiperazine	н	8-(N)-N-methyl-pyrrolidinium, I	8-(N)-pyrrolidine	8-(N)-N-methylazetidinium, I	8-(N)-azetidine	8-(N)-morpholine	8-N*(Me)2CH2CO2H, I"	8-MeCH2CO2H	8-N (CH2CH3) 2	8-NHC (-0) CH3	8-N+(CH3)3, I"	8-N (CR3) 2	8-NHCH3

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22	21	20	19	16	17	16	15	14	13	12	Ħ	5	60	80	97	90	05	04	03	02	10	A.	2	103	102	101	100	99	98	97	96	95	93	93	92	16	90	89	88
CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	Сн <sub>2</sub> Сн (он) С <sub>2</sub> н <sub>5</sub>	CH2CK (OH) C2H5	CH2CH (OH) C2H5	Сн <sub>2</sub> Сн (он) С <sub>2</sub> н <sub>5</sub>	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H3	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5		R1eR2	CH2OC2H3	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H3	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H5	CH2OC2H3
Ph-	Ph-	Ph-	₽h-	Ph-	Pb-	-44	-48	Ph-	-44	Ph-	*ÿ. -:	5 V.	Ph-	<b>8</b> 57	<b>8</b> 77	Ph-	Ph-	₽h-	Ph-	-44	8 p		75 75	Ph-	P.	Ph-	<b>P</b> h-	Ph-	₽'n	Ph-	Ph-	Ph-	Ph-	Ph-	Ph-	Ph-	P	Ph-	Ph-
7-(N)-aretidine	7-(N)-morpholine	7-N*(Me)2CH2CO2H, I*	7-NMeCH2CO2H	7-N (CH2CH3) 2	7-NEC (-0) CH3	7-N+(CH3)3, I	7-N (CH3) 2	7-NHCH3	7-инон	7-NH2	7-SCH2CH3	7-502СН3	7-SOCH3	7-SCH3	7-0(1so-propy1)	7-0CH <sub>3</sub>	7-OH .	7-tert-butyl	7-iso-propyl	7-ethyl .	7-methyl	11.00			7-SCH3, 8-SCH3	7-5CH3, 8-0CH3	7-0Сн <sub>3</sub> , 8-ОСн <sub>3</sub>	9-(2)-thiophene	9-NH-C (NH) NH2	9-NHC (0) CH2Br	9-NHC (0) C5H11	9-NH-CBZ	9-(N)-N'-dimethylpiperazinium, I"	9-(N)-N'-methylpiperazine	9-(N)-N-methyl-morpholinium, I	9-(N)-N-methyl-pyrrolidinium, I	9- (N) -pyrrolidine	9-(N)-N-methylazetidinium, I	9-{N}-azetidine

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7- (N) -N' -dimothylpiperazinium, I'

7-NHC (0) C5H11 7-NHC (0) CH2Br 7-NH-C (NH) NH2

> CK1CH (OH) C1K5 CH2CH (OH) C2HS CH2CH (0H) C2H5 CH2CH (OH) C2H5 CH2CH (OH) C2H3 CH2CH (OH) C2H5 CH2CH (OH) C2H5 CH2CH (OH) C2H5 CH2CH (OH) C2H5 CH2CH (OH) C2H5

7-NH-CB2

CH2CH (OH) C2H5

2 28 8 32 33

7-(2)-thiophene

8-methyl

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3-othyl

8-D(4so-propyl)

8-0CH3 8-9CH<sub>3</sub>

ş

-iso-propyl 8-tert-butyl

7-(N)-N-mathyl-pyrrolidinium, I'

7-(N)-N-mathylazatidinium, I

7-(N)-pyrrolldine

CH2CH (OH) C2H5 CH2CH (OH) C2H5 CH2CH (OH) C2H5 CH2CH (OH) C2H5 CH2CH (OH) C2H3 CH2CH (0H) C2H5 CH2CH (OK) C2H5

7-(N)-W-mathyl-morpholinium, I"

7-(N)-N'-methylpiperazine

8-NH-C (NH) NH2 8-(2) -th (others	hv1	ıyı	-iso-propyl	9-tert-butyl		43	9-0 (1so-propyl)	43	CH3	2CH3	9-SCH2CH3	2	ж	CH <sub>3</sub>	9-N (CH3) 2	9-N (CH3) 3, I	9-NAC(-0) CH3	9-N (CH2CH3) 2	9-NMaCH2CO2H	9-N* (Me) 2CH2CO2H, IT	9-(N)-morpholine	9- (N) -azetidino	9-(N)-N-methylazetidinium, I	(N) -pyrrolidine	(N) -N-methyl-pyrrolidinium, I	(N) -N-mathyl-morpholinium, I	(N)-N'-methylpiperatine	9-(N)-N'-dimethylpiporexinium, I	9-NH-CB2	9-NHC (O) C5H11	9-NHC (0) CH2BE	9-NH-C (NH) NH2	9-(2)-thiophena	7-осиз, 8-осиз	7-SCH3, 6-OCH3	8-SCH3	
-HZI-0	9-methyl	9-ethyl	9-130	9-16	9-0 HO-6	9-0CH3	9	9-SCH3	9-SOCH3	9-S02CH3	9-50	9-NH2	9-NHOH	9-NHCH3	Ŭ N-6	2-6	EN-6	2-6	9-K	. K6	N) -6	<u>۔</u> 2	-6 E	٦ 2	-6 Z)	<u>ا</u>	<u>د</u>	<u>ئ</u>	- K	-6	2-6	-6 -18	9-6	Ş	7-5	7-5	6-0CH3,
	. Ł	- H	-u	-q&	-ta	-ua	-ua	바	-ha	-q	i.	붑	-ua	-Hª	붑	-qa	-Ha	-u-	-ud	-u-d	-q&	-q.	Ph-	-E	-qa	-u	<b>-42</b>	-qa	- 4급	÷ č	ם	Ph-	Ph-	-dg	Ph-	-Ha	뮵
CH2CH (OH) C2H5	CH2CH (OH) C3H2	CH2CH (0H) C2H3	CH2CH (OH) C2H3	CH2CH (0H) C2H3	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OK) C2H3	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH <sub>2</sub> CH (OH) C <sub>2</sub> H <sub>5</sub>	CH2CH (OH) C2H3	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (0H) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (0H) C2H5	CH2CH (0H) C2H3	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH2CH (OH) C2H5	CH,CH (OH) C,H4	CH2CH (OH) C2H3	CK2CH (OH) C2H3	CH,CH (OH) C,H5
59	: 6	89	69	20	נג	72	73	74	75	16	11	78	79	. 08	81	82	83	84	88	98	67	88	68	96	16	92	93	93	98	96	97	98	66	100	101	102	103

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8-(N)-N'-dimethylpiperazinium, I'

8-NRC (0) C5H11 8-NEC (0) CH2Br

8-NH-CB2

CH2CH (OH) C2H3 CH2CH (OH) C2H3

CH2CH (0H) C2H5

8-(N)-N-methyl-pyrrolidinium, I-

8-(N)-N-methylazetidinium, I-

CH2CH (OH) C2H5

8-(N)-pyrroliding

8-N\* (Me) 2CH2CO2H, IT

8-N+(CH3)3, I"

CH2CH (OH) C2H3

CH2CH (OH) C2H5 CH2CH (0H) C2K5 CH2CH (OR) C2H5 CH2CH (OH) C2H5

2 2 2 š 56 57 28 53 8 19

8-N(CH3)2

8-NHCH3

8-NHOH 8-NH2

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8-SCH2CH3

CH2CH (0H) C2H5 CH2CH (0H) C2H5 CH2CH (0H) C2H5 CH2CH (OH) C2H5 CH2CH (0H) C2H5

8-502CH3

8-SOCH3

CH2CH (OH) C2H5 CH2CH (OH) C2H3

0

8-N (CH2CH3) 2

8-NHC (=0) CH<sub>3</sub> 8-NM&CH2CO2H 8-(N)-morpholine

8- (N) -azetidine

8-(N)-N-methyl-morpholinium, I-

8-(N)-N'-methylpiperazine

CH2CH (0H) C2H5

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39	24		37	36	35	34			: :	بب	16	30	29	28	27	26	25	24	23	22	21	N	_	· .	_		_	_	_		_	_	_	_	_	_					F101.011	(TTT, xxx.		
																						20	19	18	17	Ó	í,	1	13	12	#	10	9	8	07		20	04		: 5	3 5	٦	\$	
CH20- (4-picoline)	CH20- (4-picoline)	on of the protection of the	H-O- (A-nina) ()	CH20-(4-picoline)	CH20- (4-picoline)	CH20- (4-picoline)		CH20-(4-picoline)	culo-(#-breatine)	"Hade (A principles)	CHyO- (4-picoline)	CH20- (4-picoline)	CH20-(4-picoline)	CH20- (4-picoline)	CH20- (4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20- (4-picoline)	CH20-(4-picoline)	CH2O- (4-picoline)	CH20- (4-picoline)	CH2O- (4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH <sub>2</sub> O-(4-picoline)	CH2O- (4-picoline)	CH20-(4-picoline)	CH20- (4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20- (4-picoline)	CH20-(4-picoline)	CH20- (4-picoline)	CH20- (4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20- (4-picoline)		R <sup>1</sup> =R <sup>2</sup>	
•	<b>Ph</b> -	- n	,	9	7	-44		<b>P</b> h-	<b>P</b> h-	1	g ;	7	2	2	P 5-	P.	Ph-	Ph-	7	7	P 7	P.	P.5-	P.5-	<b>8</b> 1-	24	₽ 1,-	₽ħ-	<b>79</b>	Ph-	<b>P</b> 7	Ph-	-44	Ph-	Ph-	₽.	-48	Ph-	Ph-	Ph-	Ph-		75 55	
B-OCK;	8-0H	d-teart-buty!			8-ethy]	0-methyl		7-(2)-thiophene	7-NK-C (NH) NH2	/=NRC(U) CH2BE		7-NHC (0) Coll.	7-NH-CBZ	7-(N)-N'-dimethylpiperatus	7-(N)-N'-methylpinersein	7-(N)-N-methyl-morpholini T	Fro14d4n4	7-(N)-pyrrolidine	7-(N)-N-methylazetidinium, I-	7-(N)-azetidine		7-N+(Me);CH2CO2H, I-	7-NMeCH2CO2H	7-N (CH2CH3) 2	7-NHC (=0) CH3	7-W+ (CH3) 3, I	7-N(CH3)2	7-NECH3	7-NHOH	7-NH2	7-SCH2CH3	7-SO2CH3	7-soch <sub>3</sub>	7-SCH3	7-0(iso-propyl)	7-OCH3	7-OH	7-tert-butyl	7-iso-propyl	7-ethyl	7-methy1		(R≚)g	
80	. 79	70	78	77	76	75	: 3	1 :	<b>.</b>	72	71	70	69	68	67		66	55	. 64	63	62	. 61	60	59	58	57	56	\$5	54	ន	52	51	50	49		; ;	: \$	: :	. 1		A #	5 :		
CH <sub>2</sub> O-(4-picoline)	CH2O-(4-picotine)	CH-O- (A-Dicoline)	CH <sub>2</sub> O-(4-picoline)	CH20-(4-picoline)	CH20- (4-picoline)	CH20- (4-picoline)	cuio-(a-breatme)	Cupo- (4-picolina)	CH-O- (4-picoline)	CH <sub>2</sub> O- (4-picoline)	CH2O- (4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH <sub>2</sub> 0-(4-picoline)	CH20- (4-picoline)		CH20- (4-picoline)	CH20- (4-picoline)	CH20- (4-picoline)	CH2O- (4-picoline)	CH2O- (4-picoline)	CH20- (4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH2O- (4-picoline)	CH20-(4-picoline)	CH2O- (4-picoline)	CH2O- (4-picoline)	CH20- (4-picoline)	CH2O- (4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH <sub>2</sub> O- (4-picoline)	CH20-(4-proortne)	CH2O-(4-picoline)	Cm20-(4-preoring)	cm20-(4-picolina)	CH <sub>2</sub> O- (4-piceline)	CH-O- (A-picoline)	CRa0- (4-picoline)	CH_O- (4-picoline)	CH20-(4-picoline)	
P	70-	9	-4g	Ph-	<b>P</b> h-	- 4 &		ş :	ا ا	P 7	-44	Ph-	3	- P	Ph-		719	100	2	P	PA-	7	5µ-	Ph-	P	Par	Ph-	Ph-	Ph-	<b>9</b> h-	2	-44	Ph-	- U.S.	1		1		7 :	·	? :	7	7 7	
9-NHCH3	y-MAOA	9-NHOH	9-NH2	9-SCH2CH3	9-S02CH3	9-SOCH3	3 3003	9-SCH2	9-0(iso-propyl)	9-0CH3	9-0H	9-tert-butyl	9-iso-propyl	9-ethyl	9-methyl		8-(2)-thiophene	B-NH-C (NA) NH2	8-NHC (O) CH2Br	8-NHC (0) C5H11	8-NH-CBZ	8-(N)-N'-dimethylpipezazinium, I"	8-(N)-N'-methylpiperazine	8-(N)-N-methyl-morpholinium, I	8-(N)-N-methyl-pyrrolidinium,	8-(N)-pyrrolidine	8-(N)-N-methylazetidinium, I	8-(N)-azetidine	8-(N)-morpholine	8-N* (Me) 2CH2CO2H,	8-MeCH2CO2H	8-N (CH2CH3) 2	8-NHC (=0) CH3	8-N*(CH3)3, I	0-0/Cn3/2	B-WCH3	8-MICH	Pun's	B-NB2	8-80408-	B-soocha	B-SOCH-	8-0(iso-propy1)	

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-1 -6 (CH2) -N-6	9-NHC (=0) CH3	9-N (CH2CH1) 2	9-NMCHOCKOCK	9-N*(He),CH2CO2H, TT		9-(N)-azetidine	9-(N)-N-methylasetid(nimm r-		9-(N)-N-methyl-pyrrolidinim r-	9-(N)-N-methylmomboltation	9-(N)-N'-methylpiperazina	9- (N) -N' -dimethylpforereistra		9-NHC (Q) C5H11	9-NHC(0)CH3BF	9-NH-C (NH) NH	9-(2)-thiophene	7-0CH1, 8-0CH1	7-SCH3, 8-OCH3	7-5CH3, 8-5CH3	6-осиз, 7-осиз, 8-осиз
-ra	, E	- ta	-44 -44	Ph-	-Hª	Ph-	-48 -48	-ua	-ua	-da	-4ª	-40	-44	Ph-	-ua	-d	Ph-	- H	- H-	Ph-	-Ha
CH30-(4-picoline)	CH20- (4-picoline)	CH <sub>2</sub> O-(4-picoline)	CH20- (4-picoline)	CH <sub>2</sub> O-(4-picoline)	CH <sub>2</sub> O-(4-picoline)	CH <sub>2</sub> O-(4-picoline)	CH20-(4-picoline)	CH <sub>2</sub> O-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH <sub>2</sub> O-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20-(4-picoline)	CH20- (4-picoline)	CH <sub>2</sub> O-(4-picoling)	CH <sub>2</sub> O-(4-picoline)	CH <sub>2</sub> O-(4-picoline)	CH <sub>2</sub> O-(4-picoline)	CHyO-(4-picoline)
82	83	8	92	98	81	88	68	8	16	92	66	93	8	96	97	86	55 55	100	101	102	103

Additional Structures of the Present Invention

-H- 4 2 4	<b>≱</b> H
FR	(H)
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	<b>1</b> 0

Onima-C	н	-hydroxyphenyl	H	HO	e(pk)	[Ainq-u	111
7-acetanido	Н	byenyl	T H	Ю	JAinq-u	сірід	011
onima-7	н	4-(qec\jnx\)bpeu\j	Н	HQ	I/tinq-u	ethyl	601
(obimalyxah)-7	Н	byenyl	H	но	J/Jnq-u	ethyl	801
onima-7	н	4-(qechipxh)byenhj	T H	НО	ethyl	lynd-n	<b>201</b>
7-(2'-bromoscetamido)	н	byeukj	T H	НО	(V)ud-n	ετρλη	901
7-methanesulfonamido	Н	ρίνουλί	1 · H	HO	l/hud-n	cthyl	501
Onimethylamin-7	Н	byeuλj	H	НО	[Anq-u	erpkj	MI
7-thmethylammonium iodide	Н	phenyl	H	НО	αιγλ <u>ι</u>	lysud-n	103
>-t-dinethylammunium lodide	н	bysuk)	H	НО	Jáng-u	ецил	701
miliang S and In	н	byeuλj	Н	НО	lĶīnq-u	ειμλι	101
( <sub>K</sub> .)	к	В,	В	Вэ	В	- K1	Compound

- 1	112	ethyl	n-butyl	ОН	Н	2,1	Н	7-amino
						H <sub>2</sub> N OH		
	113 114	ethyl ethyl	n-butyl n-butyl	OH OH	H	4-hydroxyphenyl	н Н	7-amino 7-amino
-	115	n-butyl	ethyl	<del>oii</del>	<del>l ii</del>	4-methoxyphenyl		
-	116	ethyl	n-butyl	OH	<del>  H</del>	4-methoxyphenyl	Н	7-(O-benzylcarbamato)
-	117	n-butyl	ethyl	OH OH	H	phenyl phenyl	H	7-(O-benzylcarbamato)
-	118	ethyl	n-butyl	<del>on</del>	Fi		H	7-(O-benzy lcarbamato)
۵ <del>۱</del> −	119	ethyl	n-butyl	<del>OH</del>	H	phenyl	Н	7-(O-benzy karbamato)
°	120	n-butyl	ethyl	OH	ਸ	phenyl	Н	7-(O-tert-butylcarbamato)
<u> </u>	121	ethy)		OH		phenyl	Н	7-(O-benzykarbamato)
<u> </u>	122		n-butyl		H	phenyl	н	7-amino
		n-butyl	ethyl	OH	H	phenyl	н	7-amino
	123	ethyl	n-butyl	OH	H	phenyl	H	7-hexylamino
<u> </u>	124	n-butyl	ethyl	OH	H	phenyl	H	7-(hexylamino)
	125	ethyl	n-butyl	OH	н	pheny!	н	7°4-1, MCH1P
ŀ		ì				•	I	at the 8-position
	126	n-butyl	ethyl	он	H	4-fluorophenyl	н	7-(O-benzylcarbamato)
	127	n-butyl	ethyl	OH	H	4-fluorophenyl	H ·	7-amino
	126	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-(O-benzylcarbamato)
	129	ethyl	n-butyl .	OH	H	4-fluorophenyl	Ĥ	7-amino
	131	ethyl	n-butyl	он	н	4-Huorophenyi	н	at the 7-position

				T 571	7 - 77 -		-	
	132	ethyl	n-butyl	ОН	Н	phenyl	н	CL/1/2
								at the 8-position
	133	ethyl	n-butyl	ОН	н	phenyl	H	8-(hexyloxy)
	134	ethyl	n-butyl	OH	н	phenyl	Н	at the 8-position
	135	ethyi	n-butyl	OH	H	phenyl	н	at the 8-position
1	136	ethyl	n-butyl	OH	H	phenyl	H	8-hydroxy .
	137	n-butyl	ethyl	OH	н	phenyt	н	JOHN!
4	138			ОН	н			at the 7-position
	139	n-butyl	ethyl	OH	뀨	phenyl	Н	8-acetoxy
	139	n-butyl	ethyl	OH	п	phenyl	н	at the 7-position
	140							
- 1	141	- 4						
1	142	ethyl	n-butyl	Н	он	E	3-methoxy- phenyl	7-methylmercapto
- 1	143	ethyl	n-butyl	OH	н	3-methoxyphenyl	н	7-methylmercapto
Ĩ	144	ethyl	n-butyl	OH	H_	4-fluorophenyl	Н	7-(N-azetidinyl)
[	262	ethyl	n-butyl	OH	н	3-methoxyphenyl	H	7-methoxy
	263	ethyl	n-butyl	н	OH	H	3-methoxy-	7-methoxy
-								

onima-5	н і	~ ~	н і	но	լ/կոգ-ս	ειμλι	567
7-dimethylamino	н	phenyl	Н	НО	1king-u	J/Jmq-u	364
onimalyznad-7	Н	lynariq	H	ю	ի/ինն-ո	lytud-n	262
onime-T	H	4-thorophenyt	Н	НО	l/dud-n	N-pnik	767
7-(O-benzykanhamato)	H	phenyl	. H	Ю.	lytud-n	lyind-r	167
onima-7	Н	ργευλί	. Н	HQ	lytud-n	Jásna-u	290
onima-5	Н. П.	phenyl	.LH	HQ	l/trag-u	lytud-n	697
onima-7	Н. Н.	byсиλլ	L H	но	lydaen	methyl	885
onima-7	Н	phenyl	H	НО	ethyl	ethyl	787
(Usennednas/yznod-O)-?	н	ργευχι	Н	HO	ειμλη	sthyl	786
		MISSING					285
(onitoAqram-')-C	н	lymidguioul)->	H	OH	lytud-n	(Yrly)	784
	byenyt						
7-methyl	-ason))-+	н	HO	H	Nind-n	ειμλι	783
lydism-7	н	lymidgroull-6	H	HQ	[Aşnq-u	cthyl	282
7-methylmercapto	н	4-(luoropheny)	H	HO	lytud-n	cthyl	281
Ysortham-Y	Н	lymadqramil-5	. Н	HO	Ninden	ειρλί	2140
Y-methuxy	н	lynaliquanili-C	HO	Н	lytud-n	tylis	SCZ
Y-ronion-Y	н	Z-liuorophenyl	HQ	Н	(A)nq-u	ειμλι	827
Yxodism-7	Н	lymadquoull-E	Н	HO	lysud-n	είγχη	117
oroull-7	н1	3-methoxyphenyl	Н	НО	[ÁInq-U	crpyl	576
	phenyl		j				
otouñ-7	-үхолэт-б	HH	HO_		lytud-n	ethyl	5/2
osony-4	Н 1	4-fluorophenyl	H	HQ	l/ling-u	cthyl	727
	phenyl						
oroull-7	-orouli->	B	HO	_#_	lytud-n	εεμλι	ELZ
	phenyl	•			ս-բունյ	εινλη	242
umord-Y	-vxorhsm-E		HO		LUNG-U	erph <sub>l</sub>	142
omend-7	<u> </u>	lynadqyxudlam-E	н_	HO	frind-n	εινή	220
γκοι φάνη-ζ		lymangarouli-A		HO	fetted-a	Pale	UZC
f	phenyl	••	اميرا		n-prikj	егрλј	692
Yxorlam-7	-oiouli-	4-thoruphenyl	HO	HO -	Lynd-n	IAUJA	598
Yxorhsm-7	— н	γευντικότης γ		HO	lyind-n	ειγλι	492
Yxoriam-7	- <del></del>	3-μλαιοχλάμευλι	<del></del>	_HO	n-butyf	ειγλ	592
γχαι έγή-ζ	H byeuki	hrandouvmbusLf				135	7/6
	methyl-		[ ]			( I	
V-methoxy	-cnoullint-E	u	но	н	րչիսգ-ս	ειμλη	592
Y-methoxy	H	3-trilluoromethylphenyl	- H	H9	L/ung-u	ειγλ	197
Wardiamer T	byeuki			-102			

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1005

1006	n-butyl	n-butyl	OH	Н		Н	7-dimethylaminu
					\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\	"	7-aimetnylamino
1007	n-butyl	n-butyl	ОН	<del>  H</del>	Br-	<del>- н  </del>	7-dimethylamino
					1. N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>		,
1008	n-butyl	n-butyl	ОН	H	٠, ١, ١, ١, ١, ١, ١, ١, ١, ١, ١, ١, ١, ١,	н	7-dimethylamino
1009	n-butyl	n-butyl	OH	н		н .	7-dimethylamino
1010	n-butyl	n-butyl	ОН	-н	3-fluoro-4-methoxyphenyl		
1011	n-buty!	n-butyl	OH	Ĥ	3-fluoro-4-(5-triethylammoniumpentyloxy)phenyl, trifluoroacetate salt	H	7-dimethylamino 7-dimethylamino
1012	n-butyl	n-buty!	OH	H	4-hydroxyphenyl	H	7-dimethylamino;
1013	n-butyl	n-butyl	OH	н	+ L N(CH <sub>3</sub> ) <sub>3</sub>	н	9-methoxy 7-dimethylamino
1014	n-butyl	n-butyl	OH	H	4-methoxyphenyl	н	7-dimethylamino; 9-methoxy

	1015	n-butyl	n-butyl	ОН	н	Br. D	н,	7-dimethylamino
	1016	n-butył	n-butyl	ОН	Н	1, co, H	· H	7-d imethylamino
	1017	n-butyl	n-butyl	он	н		н	7-dimethylamino
4	1018	n-butyl	n-butyl	ОН	Н			7-dimethylamino
	1019	n-butyl	n-butyl	OH	н	(CH <sub>2</sub> ) <sub>4</sub> (CH <sub>2</sub> ) <sub>4</sub> (CH <sub>2</sub> ) <sub>4</sub>	н	7-dimethylamino
}	1020	n-butyl	n-butyl	OH	Н	C. **N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>1</sub>	Н	7-dimethylamino

onimatydismib-7	Н	HO STATE OF THE ST	н	ю	(Ainq-u	JÁINQ-U	EZOI
onimalydismib-Y	н	HO (1)	Н_	НО	įkiną-u	[ʎɪnq-u	2Z01
onimalydr <del>sm</del> ib-Y	Н		н	но	lyind-n	u-paik]	1201

								-
unimalydэmib-7	Н	HO TO	Н	но	įkiną-u	lyind-n	* #201	
onimalytismi b-7								
onimelydiamib-7	н	<del></del>	Н_	НО	lytud-n	lyind-n	2701	ł
onimelydramib-V	н		н	Ηo	lķing-u	ių:ud-n	A <u>5</u> 01	72
			-7-	-60	Interest	100.04	700.	4
7-dimenhylamino	н	Michigh?	Ħ	но	JÁJnq-u	lytud-n	SZOL	
·								
unimalydiəmib-7	н		<u> H [</u>	но	lysud-n	ս-բուհյ	1054	ł

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1				1		Н	7-dimethylamino
1030	n-butyl	n-butyl	OH	H		 	
							7-dimethylamino
				н	(CH <sub>2</sub> ) <sub>4</sub> (CH <sub>2</sub> ) <sub>5</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>5</sub>	н	7-dimethylamino
					Gr.co., +	н	7-d imethylamino
						А	7-dimethylamino
		n-outy)	OH	н		н	7-dimethylamino
		•					
	1031	1031 n-butyl 1032 n-butyl	1031 n-butyl n-butyl  1032 n-butyl n-butyl  1033 n-butyl n-butyl	1031 n-butyl n-butyl OH  1032 n-butyl n-butyl OH  1033 n-butyl n-butyl OH  1034 n-butyl n-butyl OH	1031 n-butyl n-butyl OH H  1032 n-butyl n-butyl OH H  1033 n-butyl n-butyl OH H	1031 n-butyl OH H  1032 n-butyl n-butyl OH H  1033 n-butyl n-butyl OH H  1034 n-butyl n-butyl OH H  1034 n-butyl n-butyl OH H  1035 n-butyl n-butyl OH H  1036 n-butyl n-butyl OH H  1037 n-butyl n-butyl OH H  1038 n-butyl n-butyl OH H	1031 n-butyl n-butyl OH H  1032 n-butyl n-butyl OH H  1033 n-butyl n-butyl OH H  1034 n-butyl n-butyl OH H  1034 n-butyl n-butyl OH H  1035 n-butyl n-butyl OH H  1036 n-butyl n-butyl OH H  1037 n-butyl n-butyl OH H  1038 n-butyl n-butyl OH H

	1035	n-buty <b>i</b>	n-butyl	OH	H		H	7-dimethylamino
ا د	1036	n-butyl	n-butyl	OH	H	COLCHEN,	н	7-dimethylamino
첫	1037	n-butyl	n-butyl	ОН	H	4-hydroxyphenyl	н	7-dimethylamino
	1038	n-butyl	n-butyl	OH	н	1. n(CH <sub>3</sub> ) <sub>3</sub>	н	7-dimethylamino
⊢	1039	n-butyl	n-buty!	OH	н	phenyl	H	7-dimethylamino
	1046	n-butyl	n-butyl	он	H	(CH <sub>2</sub> ) <sub>4</sub> (CH <sub>2</sub> ) <sub>4</sub> (CH <sub>2</sub> ) <sub>4</sub> (CH <sub>2</sub> CH <sub>2</sub> ) <sub>3</sub>	Н	7-d Imethylamino
- 1					l i	???How does this differ from 73281?	1	

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onimelyd <del>is</del> mib-7	н		н	НО	l⁄ting-u	ւ լճյոգ-ս	<b>750</b> t	
		, a, co, i						
onimalydismib-V	н		_Н_	НО	fytud-n	lytud-n	LSOL	₽,
onimskythomi b-7	Н		Н	но	lų ind-n	lųind-n	_0501	
onimely/lamib-Y	н_		н	но	j/inq-u	fysuc-n	6101	
		1 (CH,CH,CH,S)						
onimalydssmib-5	н	. ~ /	н	но	lyind-n	ບ-ຄຸດເຈ້ງ	81-01	]

		Lo Lo Michigan	7	T	T	T	T	7
onimelydismib-7 onimelydismib-7	<u> </u>		Н	но	jáing-u			
	<del>                                     </del>	lynadqonima-6	L H	HO	lylud-n	lytud-n lytud-n	201 201	-1
onimelyhylamib-7	Н	C(CH <sup>2</sup> ) <sup>2</sup> CL <sup>2</sup> CO <sup>2</sup> .	н	но	JÁsnq-u	րերոգ-ս	Shot	
Orimely/damib-7	Н :	N(CH*CH*P)	н	НО	JÁING-U	n-butyl	#01	
, avimalydismib-7							7701	1
neimelydismib-7	Н	/ / /	lн	НО	u-path)	[Á]nq-u	E101	1
ဝင်္ကဏနှုန်ပျံခဏ[ဥ-၇	H.	I- M(CeMe)	н		Į (ling-u			
			H	HQ.	JAINQ-U	182па-и	Zhoi	
onimatydramib-X	н	4 1	- 1		- 1	l l		l

	9053	n-butyl	n-butyl	OH	111	→ CΓ,∞,·	H	· 7-dimethylamino
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	l		1		1	O CCH 2 P		
		}	ĺ			<b> </b>	Ì	
	1	ł			1	N-		
	1054							
•	1054	n-butyl	n-butyl	ОН	H	4	н	7-dimethylamino
	· .		1					
		j	į					
	1055	n-butyl	n-butyl	ОН		l° J <sub>3</sub>	н	7-dimethylamino
			,		"		"	7-unemylamino
∞								
·	1056	n-butyl	n-butyl	он	н	J	- н	7-dimethylamino
				ľ				
- 1	1057	n-butyl	n-buty!	он	н	<u> </u>		
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. [	1058	n-butyl	n-butyl	ОН	н	Jan Jan	н ,	7-dimethylamino
ļ	1059	n-butyl	n-butyl	OH	н	Br. Dr.	н	7-dimethylamino
ŀ	1060	ethyl	n-butyl	OH -	H	3-fluoro-4-methaxyphenyl	H	7-methylamino
ಭ	1061	n-butyl	n-butyl	OH OH	н		н	7-methylamino
	1062	n-butyl	n-butyl	ОН	н		н	7-methylamino
	1063	n-butyl	n-butyl	ОН	H		н	7-methylamino

unimelydismib-V	н	3-իչժուդչոուիչինիարչի	Н	но	lylud-n	fyind-n	<u>//01</u>
		- t + t + t + t + t + t + t + t + t + t					
unimalydismib-C	н		Н	но	[Ang-u	լչուգո	9/01
orimely/lamin-9			T		n-pniyl	ո-եսեչ)	SZ01
7-dimethylamino;	H	3-fluoro-4-methoxyphenyl 4-fluorophenyl	1 #	HO	n-butyl	etpki	1/01
onimalydismib-7	l H	, I Br.	l H	но	լկոգս	lyind-n	E40L
onimely/its-mib-7	н	HO I I	н	но	lyind-n	լենոգ-ս	<b>ረረ</b> 01
onime!yd1=mib-7	H		Н	HO	<u> Kunq-u</u>	Į King-u	1201
onimelydasmib-7	н	0,000		но	lyibd-n	լչնոգ-ս	0/01

conimalydismib-7 onimalydismib-9								_
Conimalydamib-7	Н	ьренд	Ĺн	но	l/inq-u	լչնիդ-ս	6901	7
onimalydismib-V	Н		н	НО	JÁ3nq-u	Iking-u	9901	
animeludtamib-V	НН	ly-E-narlqoirla	H	HO	γίης-υ	l/inq-u	4901	1
onimal\(\psi\rightarrow\)	Н		н	НО	lýsuď-n	14jnq-u	9901	83
onimelydssaub-V	н	((cH³CH²CH²CH²O)³CH²)²	н	но	į/inq-u	lyind-n		
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	·					·		
onimalydism-5	н	$\smile$ 1	н	но	ı£ıng-u	u-pari)	94507	l

1080 a-butyl n-butyl OH H 7-dimethylan	1078	ethyl	n-buty!	NO.	H.	4-hydroxyphenyl	H	7.41
1081 n-butyl n-butyl OH H 7-dimethylar	1079	ethyl	n-buy!	ОН		O S OH	H	7-dimethylamino 7-dimethylamino
1081 n-butyl n-butyl OH H 7-dimethylam	1080	n-butyl	n-butyl	ОН	н		H	7-dimethylamino
	1081	n-butyl	n-butyl	ОH	H		н	7-dimethylamino
1082 n-butyl n-butyl OH H 2-pyridyl H 7-dimethylani	1082	n-butyl	n-buty)	ОН	н	2-pyridyl		7-dimethylamino

	1083	n-butyl	n-butyl	ОН	н		н	7-dimethylamino
	1084	n-butyl	n-butyl	он	н		н	7-dimethylamino
- 1	1085	n-butyl	n-butyl	OH	н	thiophen-3-yl	н	7-dimethylamino
82	1086	n-butyl	n-butyl	ŎĤ.	H	Jan. K.	н	7-dimethylamino .
Ī	1087	n-butyi	n-butyl	он	H	, , , , , , , , , , , , , , , , , , ,	н	7-dimethylamino
	1088	ethyl	n-butyl	OH	H	3,4-methylenedioxyphenyl	H	7-dimethylamino
	1089	ethyl n-butyl	n-butyl n-butyl	OH OH	H	4-methoxyphenyl	H H	7-dimethylamino
	1020	n-outys	noutyi	G.				7-dimethylamino

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onimelydramib-7	<del></del>	~ ~ ~	Н.	НО	[ƙinq-u	l/inq-u	COLL
primelydamib-X	Н_	3-corboxymethylphenyl	H	НО	lytud-n	l/linq-u	2011
onimatyds-mib-T	Н		н	но	lyhud-n	lyind-n	1011
7-dimethylamino	Н	4-methoxyphenyl	Н	죠	l/thud-n	n-bulyl	1100
Onimethylamin-	Н	-methoxyphenyl	H	Ю	Jámq-u	ethyl	6601
onimelyda <del>sm</del> ib-7	н	(ch'ch')	Н	но	lytud-n	յ <i>է</i> լոգ-ս	\$601
onimalydramib-7	Н.	,a , , , , , , , , , , , , , , , , , ,	н	но	Į/sinq-u	fKinq-u	<b>260</b> 1
	<del> </del>		-н-	HU	landa	[ntrid-0	2001
onimstyd3smib-7	н		Ħ	но	Jájng-u	<u> լ</u> անոգ-ս	9601
onimaty/dismib-7	н		u	но	Ainq-u	ly)ud-n	\$601
			_H_	LHU	lutindan	Tuturka	7001

onimalydismib-7	н .		н	НО	, Jáing-u			
			<del>  "</del>	HO	[AInq-u	fy1ud-n	1601	-
onimalydэmib-7	Н		н	НО	l⁄ind-n	JÁINQ-U	£501	7.
onimslydrsmib-7	н		н	но	(Ásnq-u	Į∕inq-u	<b>Z601</b>	
		<u></u>		114		1	cour	1
onimalyAssmib-7								
entimety/distrails-7	н		Н	НО	l/tinq-u	աթուհլ	1601	l

1104	n-butyl	n-butyl	OH	н		H	7-dimethylamino
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		1	ı	1		1 1	
j		1		1		1 1	
1105	n-butyl	n-butyl	ОН	H	13		
1106	n-butyl	n-butyl	OH	<del>                                     </del>	5-piperonyl 3-hydroxyphenyl	H	7-dimethylamino
1107	n-butyl	n-butyl	OH	H		+ # +	7-dimethylamino
ŀ		1	ı		↓ Br <sup>−</sup>	"	7-dimethylamino
ŀ		į	1	l		1 1	
	ı	ĺ	1	1		1 1	
	-	l ·				1 1	
1108	n-butyl	n-butyl	OH	Н			
1109	n-butyl	n-butyl	<del>  on</del>	ਜਿ	3-pyridyl	H	7-dimethylamino
		1	"	1 "	√ F	H	7-dimethylamino
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			1	1 1		1 1	
1110	n-butyl	n-butyl	ОН	H		н -	7-dimethylamino
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iiii	n-butyl	n-butyl	ОН	H	' '3	,	
		•			· Start area.	н	7-dimethylamino
	1 1		1 1				
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	1 1			- 1	COTH COTH	i	
1112	n-butyl	n-butyl	OH	H	4-pyridyl	H	7-dimethylamino
							, - amietity turnino

	1113	n-butyl	n-butyl	ОН	н		Н .	7-dimethylamino
	1114	n-butyl	n-butyl	ОН	н	3-methoxyphenyl	,	7-methylamino
-	1115	n-butyl	n-butyl	OH	H	4-fluorophenyl 3-tolyl	Ĥ	7-dimethylamino
	1116	ethyl	n-butyl	ÖН	H	3-tolyl	н	7-dimethylamino
	1117	ethyl	n-butyl	ОН	H	1- 1- 1- N(CH <sub>2</sub> ) <sub>3</sub>	н	7-dimethylamino
- 1	1118	ethyl	n-butyl	OH	뉴	3-fluoro-4-hydroxyphenyl	H	7-dimethylamino
g.	1119	n-butyl	n-butyl			the state of the s	н	7-dimethylamino
	1120	n-butyl	n-butyl	он	Н		н	7-dimethylamino
	1121	n-butyl	n-butyl	он	Н	J. J.	н	7-dimethylamino

7-dimethylamino

WO 97/33882

PCT/US97/04076

(Ang-u

lyjud-n

onimalydism (lydismyxodis)-\ onimalydism-\ yxodism-\delta	3-methoxyphenyl	<del>  H</del>	HO	J/ynq-u	fying-u	SSIL	
onimslydtsm-Y			НО	JAInq-u	lytud-n	ISII	7
	(-(Inoropheny)	1 #	HO	J/Jnq-u	(Ainq-u	esit	1
	lynand	<del>  H</del>	НО	JÁING-U	(Ainq-u	1125	1
Onimely/dismib-7	3-fluoro-4-methoxyphenyl	<del>  H</del>	НО	etphj	Jámq-u	işii	7
onimalyhmenhyhm-7 H	3-methoxyphenyt	1 #	HO	J/4nq-u	Jámq-u	0511	1
unimelydis-7	lynshqmusii-s	H	HO	JAing-u	l\tinq-u	6711	1
H 7-dimethylsultonium, fluoride salt	4-fluncophenyl	H	НО	J/LING-U	Jáing-u	8711	1
Onimalydisib-7	3-тепрохурмену!	1 #	но	[/inq-u	Jámq-u	Z+11	1
	CCH2)10 (CCH2)2			, lýrud-n	ikina-n	9011	
	- Constitution -	H.	HO		Jáng-u	5711	1
	4-methoxyphenyl	14	НО	l/thd-n	lynd-n	3711 9911	1
		Н	НО	Landen	Intiride	PPIL	-1
enyl		1		ì			1
onimelydlamib-7 -b-010		но	l H	[/inq-u	Iking-u	EPIL	1
onimalydismib-7 H	2(PAC)AVO)IN S	H	но	lkind-n	լմյոզ-ս	1145	9
onimalydis-C H onimalydis-C H	4-(Iuorophenyl	Тн	HO.	[/Únq-u	lylud-n	trii	J
H \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	3-тегьохурьелу!	Н	но	lyind-n	lyjud-n	1140	4
. onimely/lamin-7 H	lynadqoroullib-A,E	Н	HQ	J/unq-u	lyiud-n	6811	4
(onixerbyflyfdamib-Y, Y)-2 H onimalyflamib-Y H	X Control of the second of the	Н	но	lyind-n	1/vind-n	<b>9</b> £11	
H 9-(2', 2'-dimethylhydazino)	Ivestophenyl	Н	но	l/md-n	lytud-n	LEIL	4
			•				
H 7-dimethylamino		١.,	НО	ս-բունլ	ս-բուλլ	9611	1
onimaly/thamib-7 H onimaly/thamib-7 H	Iynadqyxodamib-4,6	H	110	IVIU-n	lyind-n	SELL	1

1156	n-butyl	n-butyl	OH	T-H-	4-fluorophenyl	H	
	n-butyl	n-butyl	ОН	H	4-fluorophenyl	<del>- H</del>	7-methylmercapto 7-fluoro:
1158	n-butvi	n-butyl	OH	<del>  H  </del>			9-dimethylamino
1159	n-butyl	ethyl	T OH	┪╫┪	4-pyridinyl, hydrochloride salt	н	7-methoxy
1160	n-butyl	n-butyl	<del>  on</del>	<del>  #  </del>	phenyl	H	7-dimethylamino
1161	n-butyl	n-butyl	OH	<del>  ਜ  </del>	4-fluorophenyl	H	7-diethylamino
1162	n-butyt	n-butyl	OH	┪╫┪	3,5-dichloro-4-methoxyphenyl	H	7-dimethylamino
1163	n-butyl	n-butyl	1 OH		phenyl	H	7-dimethylamino
1164	n-butyl	n-butyl	OH	1 11	3-(dimethylamino)phenyl	H	7-methoxy
1165	n-butyl			H	4-pyridinyl	H	7-methoxy
1166	n-butyl	n-butyl n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-trimethylammonium iodid
1167	n-butyl	n-buty!	OH	H	3-hydroxyphenyl	H	7-trimethylammonium iodid
11/0		-		Н		H	7-dimethylamino
1168	n-butyl	n-butyl	OH	<u>_ H _ T</u>	4-hydrixyphenyl	<del>- H -</del>	712-01-1
1170	n-butyl	n-butyl	OH	LH I	pluenyl	<del>- ii -</del>	7-trimethylammonium iodid
1171	n-butyl	n-butyl	ОН	H	3-methoxyphenyl	<del>                                     </del>	8-dimethylamino
1172	n-butyl	n-butyl	OH	_H	4-(trifluoromethylsulfonyloxy)phenyl	<del>-   -    -    -    -    -    -    -   </del>	7-ethylpropylamino 7-dimethylamino
1172	n-butyl	n-butyl	OH	H	4-pyridinyl	<del> </del>	/-dimethylamino
	n-butyl	n-butyl	OH	H	4-fluorophenyi	<del> </del>	7-methoxy
1174	ethyl	n-butyl	ОН	H	3-methoxyphenyl	<del>                                     </del>	7-ethylpropylamino
1175	ethyl	n-butyl	OH	H	3-methoxyphenyl	<del>                                     </del>	7-pheny!
1176	n-butyl	n-butyl	OH	H	4-fluorophenyi	<del></del> -	7-methylsulfonyl
1177	n-buty!	n-butyl	OH	H	3-methoxyphenyl	<del>                                     </del>	9-fluoro
1178	n-butyl	n-butyl	OH.	н	3-(trifluoromethylsulfonyloxy)phenyl	<del>- </del>	7-butylmethylamino
1179	n-butyl	n-butyl	OH	H	phenyl		7-dimethylamino
1180	n-butyl	n-butyl	OH	H	phenyl	H	8-methoxy
1181	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-trimethylammonium iodide
1182	n-butyl	n-butyl	OH	H	4-(dimethylamino)phenyl	н	7-butylmethylamino
1183	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-methoxy
1184	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-ftuaro
					4-ridorophieny)	H	7-fluoro;
1185	n-butyl	n-butyl	OH	H	4-fluorophenyl	<del></del>	9-fluoro
1186	n-butyl	n-butyl	OH	H	pheny	H	7-fluoro
				1	huenki	H	, 7-fluoro;
1187	n-butyl	n-butyl	ОН	H	4-fluoropheny)	<del></del>	9-fluoro
1188	n-butyl	n-buty!	OH	<del>- 11   -</del>	4-methoxyohenyl	H	7-methyl
1189	n-butyl	n-butyl	ОĤ	<del>ii l</del>	3,4-difluorophenyl	Н	7-trimethylammonium iodide
1190	n-buty)	n-butyl	<del>OH </del>	<del>- ii - </del> -	3,4-GIIIUO/Opnenyi	H	7-trimethylammonium iodide
1191	.n-butvl	n-butyl	ŎН	<del>- ii   -</del>	2-bromophenyl	H	7-brumo
1192	n-butyl	n-butyl	<del>ऑ</del>	<del>- Ĥ -  </del>	4-(dimethylamino)phenyl	Н	7-hydroxy
1193	n-butyl	n-butyl	<del>ori</del>	<del>-17  </del>	3-(dimethylamino)phenyl	Н	7-hydroxy
					4-(2-(2-methylpropyl))phenyl	H	7-dimethylamino

1194	n-butyi	n-butyl	ОН	Н	\	н	7-dimethylamino
					"Charles Des		
1195	n-butyl	n-butyl	ОН		4-methoxyphenyl	н	7-(4'-methylpiperazin-1-yl)
1196	n-butyi	n-butyl	он	Ĥ	* '	н	7-methoxy
					H(CH2)2		
1197	n-butyl	ethyl	R3 + R4 = oxo	R3 + R4 =	phenyl	н	7-(N-methylformamido)
1198	n-butyl	n-buty	OH	H	4-(pyridinyl-N-oxide)	H	7-methoxy
1199	n-butyl	n-butyl	OH	Н		н	7-dimethylamino
1200	n-butyl	n-butyl	H OH	HO H	#	phenyl H	7-dimethylamino 7-methyl
1201	n-butyl	n-butyl	, un	ıl	n		/ -metny i

onimalydramib-V

onimalydas-7
comord-8
conimalydas-7
conimalydas-7
conimalydas-15
conimalydas-7
conimalydas-15
conimalyda

onimalyqonqoei-Y onimalydomib-Y

		N(CH <sup>2</sup> ) <sup>2</sup>					
onimalydismib-7	н	~ /\	H	НО	Jáing-u	n-butyl	6121
lynoituelyham-9	н	4-тирохурьену!	H.	HO	[Ainq-u	n-butyl	1218
omord-7 onimalydamin-7	H	-carboxybrenyl	H	HO	Jámq-u	cthyl	9171
9-Ymethyllomemido) 9-methylmetenpto	H H Ducuja	рреи) 4-тейохуррелу	H	НО	ethyl Ivind-n	[Λ]πα−υ [Λ]πα−υ	SIZI PIZI
onimalydtamib-7	methoxy-	1	1	1			
(onilodquom-'b)-U	3-fluoro-4-	НН	њ	Н	ειμλι	u-pntλj	
(dama-,y)-6	Н	-methoxyphenyl	H	НО	1/4nq-u	lytud-n	1515
		30000					
Onimaly/Annib-C	Н	′ ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` `	1 1	ا ا			
onimely/damin-7	H	4-methoxyphenyl Phenyl 2-(dimethylamino)phenyl	뷰	HO	լչնոզ-u լչնոզ-u	aphy	1121
V-dimethylamino Tynaddydamib-Y	Н	byeυλη		(XOE)	n-butyt	n-butyl fylud-n	1510
7-dimethylamin	H	4-methoxyphenyl	Li	но	lyind-n	IAINO-U	1508
	<del></del>	lynshlqorolhsib-2,5	Н	но	(Ang-u	lysud-n - Alud-n	2021
onimalydismib-7	н	B <sub>1</sub> .					
	<del>                                     </del>		н	но	lyind-n	ր-եսուջվ	1506
yxodism-C onimelydismi b-7		1100	н	но	JÆjna-u	IÁIDO-U	COT!
7-(4'-tert-butylphenyl)	H H	iynorophenyi	_H_	HO	lynd-n lynd-n	lylud-n	9021 1004
		lynizeraqiq-ç	Н	НО	lytud-n	IVitad-n	EOZI
	ł	и(сн <sup>э) 2</sup>					
		' 🗘					

Bt.

3-thiophenyl

3-chloru-f-hydroxyphenyl

3-mitruphenyl 3-methylphenyl 4-fluorophenyl 14-phenyl 2-pymolyl

Phenyl 3-methoxyphenyl lyind-n lyind-n

lytud-n

լչյոգ-ս լչյոգ-ս

Ivind-n fylud-n fylud-n fylud-n m-butyl

iyind-n heburyi

n-priyl

lytud-n

ը/փոգ-ս

N-butyl N-butyl

lylud-n lylud-n lylud-n lylud-n

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н но

H H H

н <u>но</u>

HO HO HO 1533

1221

1550

1553

1234	n-butyl	n-butyl	OH	H		HI	7-dimethylamino
	1				₩ Br <sup>-</sup>		,
					, N(CH <sub>3</sub> ) <sub>2</sub>		
1235	n-butyl	n-butyl	он	H	Y	H	7-dimethylamino
	·				N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>		
1236 1237	n-butyl	n-butyl	он	H	4-(bromomethyl)phenyl	н	7-dimethylamino
1237	n-butyl	n-butyl	ОН	Н	* Consideration in the second	Я	7-dimethylamino
1238	n-butyl	n-butyl	OH	H	***	н	7-dimethylamino
1239	n-butyl						
1239	n-outyl	n-butyl	OH	н	F Br	H .	7-dimethylamino
1240	n-butyl	n-butyl	ОН	H	4-methoxy-3-methylphenyl		
1241	n-butyl	n-buty!	OH	H	3-(dimethylaminomethyl)phenyl	H	7-dimethylamino
1242	n-butyl	n-butyl	OH.	H	To CI	H	7-dimethylamino 7-dimethylamino
1243	n-butyl	n-butyl	ОН	H	OH I	-н	7-dimethylamino

1244 1245	n-butyl	n-butyl	OH	H	3-methoxyplienyl	H	7-(1'-methylhydrazido)
1245	n-butyl	n-butyl	ОН	н	1 ' + N(CH <sub>2</sub> ) <sub>2</sub>	н	7-dimethylamino
1246	n-butyl	n-butyl	OH	H	3-(bromomethyl)phenyl	н	7-dimethylamino
1247	n-butyl	n-butyl	ОН	н	) OH	н	7-dimethylamino
1248	n-butyl	n-butyl	оH	Н	N(CH <sub>3</sub> ) <sub>2</sub>	H	7-dimethylamino
1249	n-butyl	n-butyl	OH	н	CT-CO-OH	н	7-dimethylamino
1250	n-butyl	n-butyl	OH	н	3-(dimethylamino)phenyl	н	7-dimethylamino
1251	n-butyl	n-butyl	OH	н	1-naphthyl	н	7-dimethylamino
1252	n-butyl	n-butyl	ОН	н	0 N(CH2CH3)3	H	7-dimethylamino
1253	n-butyl	n-buty!	ОH	H	OCH <sub>3</sub> (	н	7-dimethylamino
1254	n-butyl	n-butyl	он	H	Hr N+	н	7-dimethylamino

PCT/US97/04076	onimalydismib-7	н_
Ž		
	onimalydramib-7	Н
	Onimalyhymib-7	н
	ories indisasib.	
	onimalyAlamib-7	H-
1883		
87	onimelydsmib-Y	НН_
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	. •						
		· <u></u>					
onimalyAssmib-V	н		Н	НО	[kinq-u	lyind-n	1398
		Cho, chib				·	
	1 1		1		u-prikj	[kinq-u	8921
V-carboxy, methyl ester onimalyshamin-V	H H	lynoradiq-č	1#	HQ	eipli	JAing-U	1567
		OCH,					
onimely/ismib-7	H	M(CH9)*	Н	но	J/smq-u	Jáng-u	9971
onimalyqorqosi-9	H -	4-fluorophenyl	H	НО	lynd-n	lytud-n	1365
animityqorqoti-7	П. н	lymadqooull-4	I H	HO	lyind-n	[\text{\text{tuck-n}}	1564
omord-7	H	2-piperonyl	Н	HO	1/unq-u	1\tind-n	<b>E971</b>
V-dimethylamino	Н	lynadqoidi-S	H	НО	[ʎing-u	lytud-n	2921
		: 20-1-10					
onimalyAtamib-7	Н_	<i>γ</i>	L <sub>H</sub>	но	Minq-u	ικιπα-υ	1561
7-dimethylamino	н	Ιγπ•λαγχαιδγά-ξ	Н	НО	[/unq-u	IĄĄD	1560
Online!\\dimib-\\	byeuk	f Hillomophenyi	НО	H	lytud-n	ειμλι	1529
(onimaly)ud-na)-9	<b>Н</b> ——	lynariquoull->	H	HO	h/iud-n	lytud-n	1528
onimelydismib-7	1 1	byenλį	۱	но	sking-u	u-pnili	JS21
animalydramib-V ;amord-8		lynadenin-E	<del>  #  </del>	HO	u-prik)	L/Inq-u	1525
agiantladamih-F		c(cH3)s		100			

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V-dimethylismib-Y

onimaly dismin-7

onimalydamib-7

7-dimethylamino

onimelydamib-V onimelydamib-V

7-dimethylamino

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	unimalydiamib-5	н	русид	T -:-	T		1 7	
	onimalydas-8	Н.	-fluorophenyl	H	НО	u-priàj	fysud-n lysud-n	1285
	onimelydamib-5	Н.	4-υλαιοχλωεινλίρμευχί	I H	HO	jáng-u	JAjnq-u	1584
	sbiboi muinummelyilismini-7	н	3-fluoru-f-methoxyphenyl	H	HO	J/Jnq-u	ethy!	1282
PCT/US97/04076	onimalythsanib-7	Н	1110	Н	но	J/unq-u	lyind-n	1583
<b>6.</b>	onimalydləmib-Y	н	N(CH <sup>2</sup> ) <sup>3</sup>	н	но	լչնոգ-ս	JÁ1nq-u	0821
	onimaly/damib-Y	н	1 (CH <sup>5</sup> ) <sup>9</sup> CH <sup>2</sup>	Ξ.	но	lvind-n	i-pnihj	6/21
	опітівіүльтір-7	н.	I- (CH <sup>5</sup> ) <sup>1</sup> CH <sup>3</sup>	н	но	Įking-u	į king-u	9/21
g.	onimalydrami b-Y	н	CO'H CO'H	н	но	J∕unq-u	lçtud-n	
WO 97/33882	onimalydissni b-7	н	י יבאי יכאנמייי י יבאי יכאומייי: י יבאי יכאומייי:	н	но	الاستوسا	JÁinq-u	9/21

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-и—(сн<sup>5</sup>)-сн<sup>2</sup> (сн<sup>5</sup>)-сн<sup>2</sup>

и(сн<sup>2</sup>)³сн<sup>2</sup>)³ +

ce'co'.

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PCT/US97/04076

						\$ \$(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>		
	1300	n-butyl	ethyl	н	OH	н	phenyl	7-dimethylamino
	1301	n-butyl	n-butyl	OH	H	3-methoxyphenyl	phenyl H	7-trimethylammonium iodide
	1302	n-butyl	n-butyl	OH	H	3-hydroxyphenyl	H	9-hydroxy
	1303	n-butyl	n-butyl	ОН	н	O N(CH <sub>3</sub> ) <sub>3</sub>	н	7-dimethylamino
	1304	n-butyl	n-butyl	OH	H	3-methoxyphenyl	Н	77
1	1305	n-butyl	n-butyl	OH OH	H	4-fluorophenyl	<del>          </del>	7-tert-butylamino
- 1	1306	n-butyl	n-butyl	OH OH	H	4-ndoropheny/	<del>  ਜ  </del>	9-methylamino
104			•			) cFs	r	7-dimethylamino
	1307	n-butyl	n-butyl	OH	Н	н	4-methoxy- phenyl	9-(4'-morpholino)
	1308	ethył	n-buty)	ОН	н		н	7-dimethylamino
- [	1309	n-butyl_	n-butyl	OH	Н	4-methoxyphenyl .	Н	9-fluoro
	1310	ethyl	n-butyl	ОН	표	phenyl	H	7-amino
	1311	n-butyl	ethyl	OH	H	phenyl	H	7-(hydroxylamino)
- 1	1312	n-butyl	ethyl	ОН	H	phenyl	H·	&-hexyloxy
L	1313	n-butyl	ethyl	OH	규	phenyl phenyl	Н	R-ethoxy
1.	1314 1315	ethyl	n-butyl	OH -	<del>- ਜ਼ਿ  </del>	phenyl phenyl	H	7-(hydroxylamino)
L	1315	ethyl	n-butyl	_ On		pneny		7-(hexyloxy)

F SF3

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1294

1297 n-butyl

n-butyl

n-butyl он

7-dimethylamino

7-dimethylamino

7-dimethylamino

7-dimethylamino

7-dimethylamine

7-dimethylamino

7-dimethylamino

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onimaly/hamib-7	Н	4-((diethylamloolmalyhyl))-	Н	I Ho	l/inq-u	Jámq-u	SZCI
	Н	<u> </u>	$\perp_{H}$	Но	u-pnrkj	lyjud-n	1354
							, ,
onimalyAsmib-7	н		н	но	I/Unq-u	.6	
noitteoq-8 ant in unimelydiamib-7	н_		н	но	j/snq-u	lyind-n	1323
2 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2	Н	Phrankl Phrankl	н	но	canyl	JÁINQ-u	
osonij-7	H +	-drenkenyl Tynadd	Н	но	n-butyl cthyl	e4pkj	1350
7-dimethylamino	H	3-methoxyphenyl	Н	НО	Iviud-n	cthyl	6161
cleHCHA CALL		(many)	Н	НО	J/sinq-u	ethyl	PIEL
	н	byanki	н				i
γκσι bγή-δ	Н	Phenyl Phenyl	# 1	HO	αιγλη αιγλη	lyind-n	21E1

Onlinelydiamib-\( )

Onlinelyd

	1332	n-butyl	n-butyl	OH	H	<u> </u>	н	7-dimethylamino
	1333	n-butyl	n-butyl	OH	H	N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>	н	7-dimethylamino
	1334	n-butyl	n-butyl	OH	Н		н	7-dimethylamino
40	1335	n-butyl	n-butyl	ОН	н		н	7-dimethylamino
	1336	n-butyl	n-butyl	OH	н		н	7-dimethylamino

	1337	n-butyl	n-Uutyl	ОН	Н	¥	H	7-dimethylamino
1								
ı						(H <sub>3</sub> C) <sub>3</sub> N		
	1338	n-butyl	n-butyl	OH.	H	4-methoxyphenyl	Н	7-(4'-methylpiperazinyl)
	1339	n-butyl	n-butyl	ОН	н	C(CH <sub>3</sub> ) <sub>3</sub>	н	7-dimethylamino
	1340			ЯО	н			
- 1-	1341	n-butyl n-butyl	ethyl n-butyl	acetoxy	귀	5-piperonyl 3-metluxyphenyl	Н	7-methy!
E	1342	n-butyl	n-butyl	OH	H	5-piperonyl	H	7-dimethylamino
-	1343	ethyl	n-butyl	<del>OH</del>	H	phenyl	<del>                                     </del>	7-(4'-fluorophenyl) 7-amino
⊢	1344	n-butyl	n-butyl	ÖH	H	3-fluoro-4-methoxyphenyl	<del>H</del>	7-amino 7-dimethylamino
┢	1345	ethyl	n-butyl	OH	<del>- ii -</del>	phenyl	<del>                                     </del>	7-trimethylammonium iodide
T	1346	ethyl	n-butyl	ОН	Н	phenyl	H	at the 8-position
	1347	n-butyl	n-butyl	ОН	H	3-fluoro-4-methoxyphenyl	H	7-dimethylamino
	1348	isobutyl	isobutyl	OH	_H_	phenyl	H	7-dimethylamino
	1349	ethyl	n-butyl	OH	н	phenyl	н	7-dimethylamino
E	1350	n-butyl	n-butyl	OH	_н_	3-fluoro-4-methoxyphenyl	H	7-trimethylammonium iodide
	1351	n-butyl	n-butyl	ÖH	н	**************************************	н	7-d imethylamino
						CF <sub>5</sub> CO <sub>2</sub> (CH <sub>2</sub> CH <sub>2</sub> )(CH <sub>3</sub> ) <sub>2</sub> N		

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PCT/US97/04076	onimalydramib-Y	Н							]
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	21367	n-butyl	n-butyl	он	н		H	7-dimethylamino
		,						·
	1368	n-butyl	n-buty)	O⊦I	н	John Mills	14	7-dimethylamino
			n-butyl	ОН	н		H	7-dimethylaminu
الم	1369	n-butyl				John J.	н	7-dimethylamino
	1370	n-butyl -	n-buty)	OH	Н		7	Aumenyamin

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PCT/US97/04076 7-dimethylamino onimalydamin-Y и(сн<sup>3</sup>сн<sup>2</sup>)<sup>2</sup> + P-dimethylamin-V N(CH<sup>5</sup>CH<sup>2</sup>)<sup>2</sup> onimethytamib-7 Onimaly Assembly WO 97/33882 олілівіүдэтір-7

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PCT/US97/04076	onimalyrismib-7	н	To the to	н	НО	1/smq-u	, lýjnq-u		
	onimatyrismi b-7	н						5461	
			1 1 1	H.	НО	l/vind-n	Jánq-u	7/281	1
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	onlmely/dismib-7	Н		н	НО	ինյոգ-ս	լչնյոզ-ս	ZZE1	ı
			N 1						
L	ommaly/hamib-7	н		н	но	14)nq-u	14.mq-u	1461	

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7-dimethylamino

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7-dimethylamino 1359 n-butyl n-butyl 7-dimethylamino n-butyl 7-dimethylamino 1391

. N(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>

`N(CH<sup>5</sup>CH<sup>2</sup>)<sup>9</sup>

=

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n-buty)

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i	1403	n-butyl	n-butyl	ОН	H	1 12	н	7.41
	·							7-dimethylamino
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	1405	n-butyl	n-butyl	OH	н	L CO <sub>2</sub> H	н	7-d imethylamino
į	1406	n-butyl	n-butyl	OH	Н		н	7-dimethylamino

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ı	1410	n-butyl	n-butyl	ОН	H	F CO2H	н	7-dimethylamino
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ŀ	1411	n-butyl	n-butyl	ОН	H	* '0' \ '	н	7-dimethylamino
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						P(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>		
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onimaly hamin-CCH THE CHEST 127 onimaly draminonimalyhamin-7 onimalydramib-

1421	n-butyl	n-butyl	OH	TH	4	н	7-dimethylamino
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1422	n-butyl	n-butyl	ОН	H	<del>*</del>	н	7-dimethylamino
1							
					h show h		
1423	n-butyl	n-butyl	ОН	ਸ	+ n(CH2CH3)3	- н	7-dimethylamino
1424	n-butyl	n-butyl	ОН	H	, N. A.	н	7-dimethylamino
							7-timethylamins
1425	n-butyl	n-butyl	OH	н	¥ * "	н	7-dimethylamino
						].	
					N O HICH,CH <sub>3</sub> b		

1426	n-butyl	n-butyl	он	н	$\forall$	н	7-dimethylamino
					1- N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>5</sub>		
1427	n-butyl	n-butyl	OH	H		н	7-dimethylamino
1428	n-butyl	n-butyl	OH	н	The state of the s	н	7-dimethylamino
1429	n-butyl	n-butyl	OH	H	Br + N(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub>	н	7-dimethylamino
1430	n-butyl	n-butyl	OH	н	Br'	н	7-dimethylamino

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		+ b(C*H*)2						
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- I	onimaly/homib-7	н ј							

	1442	n-butyl	n-butyl	OH	H	F I PO <sub>3</sub> H	н	7-dimethylamino
-	1443	n-butyl	n-butyl	он	H	CO <sub>2</sub> H	н	7-dimethylamino
_	1444	n-butyl	n-butyl	RO	н		н	7-dimethylamino
	1445	n-butyl	n-butyl	ОН	н	SO,Na	н	7-dimethylamino
	446	n-butyl	n-butyl	он	H	Dr. Dr.	н	7-methoxy; 8-methoxy
1	447	n-butyl	n-butyl	ΟН	Я	Nu <sup>+</sup>	Я	7-dimethylamino

I	1448	n-butyl	n-butyl	OH	н	Na <sup>+</sup> So,	Н	7-dimethylamino
	1449	n-butyl	n-butyl	он	н		н	7-dimethylamino
							н	7-dimethylamino
<u>်</u>	1450 1451	n-butyl n-butyl	n-butyl n-butyl	OH OH	H	phenyl	Ĥ	7-dimethylamino
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PEG = 3400 molecular weight polyethylene glycol polymer chain

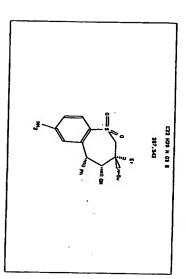
PEG = 3400 molecular weight polyethylene glycol polymer chain

PEG = 3400 molecular weight polyethylene glycol polymer chain

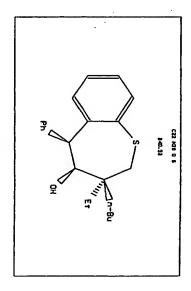
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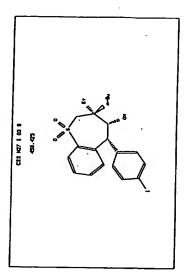


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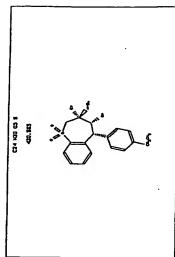


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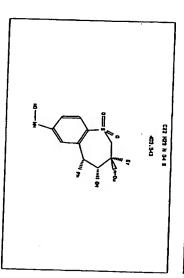
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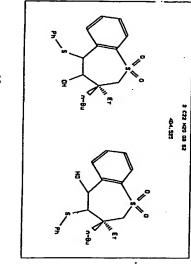
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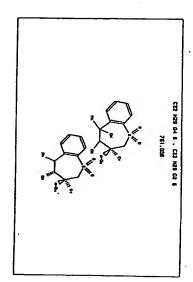


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comprises halo or a quaternary ammonium salt, alkylcarbonyloxy and arylcarbonyloxy, (0,0)substituted thereon, alkoxycarbonyl, aryloxycarbonyl, alkylene bridge having a quaternary ammonium salt N,N-dialkylamino, quaternary ammonium salts, a  $C_i$  to  $C_i$ hydroxyl, trihaloalkyl, alkoxy, amino, N-alkylamino, which the substituent(s) are selected from among halo, alkylpiperazinium, N-alkylmorpholinium, or furan in pyrazole, pyrimidine, morpholine, N-alkylpyridinium, Nthiophene, pyridine, pyrrole, thiazole, imidazole, and ring-carbon substituted or unsubstituted aryl, -[O(CH<sub>2</sub>),]X where x is 2 to 12, w is 2 or 3 and X dioxyalkylene, and R' are independently selected from among hydrogen In further compounds of the present invention, R'

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of the aryl ring. Other substituents that can be the substituents on the aryl ring of R' or R' are may be unsubstituted, mono-substituted, or dipreferably phenyl, phenylene, or benzene triyl, i.e., pyrazole, or furan. The aryl group of R' or R' is thiophene, pyridine, pyrrole, thiazole, imidazole, ring include 3,4-dioxymethylene (5-membered ring) and present on a phenylene, benzene triyl or other aromatic substituted at the p-position, the m-position, or both tetra(oxyethylene)trimethyl-ammonium iodide, each hexylenetrimethylammonium, tri(oxyethylene)iodide, and chloride counterion), methoxycarbonyl, ethoxycarbonyl, trimethylammonium (preferably with an iodide or fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, substituted. Among the species which may constitute formyl, acetyl, propanoyl, (N)-hexyldimethylammonium,

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3,4-dioxyethylene (6- membered ring). Among compounds

which have been or can be demonstrated to have desirable ileal bile acid transport inhibiting properties are those in which R' or R' is selected from

nydroxyphenyl, m-hydroxyphenyl, p-methoxyphenyl, m-

phenyl, p-fluorophenyl, m-fluorophenyl, p-

methoxyphenyl, p-N,N-dimethylaminophenyl, m-N,N-

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orientation relative to the plane of the molecule as R' and R'.

Set forth in Table 1A are lists of species of R1/R1, R1/R and R".

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dimethylpiperazinium) - (N') - CH, - (OCH, CH,), -O-phenyl, 3phenyl, I m-(CH,),-N'-CH,CH,-(OCH,CH,),-O-phenyl, I pcholorothienyl-2-yl, 3,4-difluorophenyl, I p-(N,N-

dimethylaminophenyl, I p-(CH,),-N'-phenyl, I m-(CH,),-N'-

(CH,),-N'-CH,CH,-(OCH,CH,),-0-phenyl, I'm-(N,N-

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methoxy-4-fluorophenyl, thienyl-2-yl, 5-

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fluoro-4-methoxyphenyl, -4-pyridinyl, 2-pyridinyl, 3dimethylpipexazinium) - (N') - CH<sub>1</sub>- (OCH<sub>2</sub>CH<sub>1</sub>), -O-phenyl, 3preferred R' substituents in combination with the R' Preferred compounds include 3-ethyl-3-butyl and 3substituents shown in Table 1. It is particularly dioxyethylenephenyl, and p-methoxycarbonylphenyl. outyl-3-butyl compounds having each of the above pyridinyl, N-methyl-4-pyridinium, I'N-methyl-3preferred that one but not both of R' and R' is pyridinium, 3,4-dioxymethylenephenyl, 3,4hydrogen.

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the plane of the molecule, i.e., both in a- or both in 8-configuration. It is further preferred that, where hydrogen, that R' and R' not be hydrogen, and that R' and R' be oriented in the same direction relative to It is especially preferred that R' and R' be R' is butyl and R' is ethyl, then R' has the same

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Table lA : Alternative R groups

$$\begin{array}{c}
(R^2)q \xrightarrow{\Gamma_1} \\
(R^2)q \xrightarrow{\Gamma_2} \\
R^3 \\
R^4
\end{array}$$

$$\begin{array}{c}
R^1 \\
R^2
\end{array}$$

																					-			CB-O-(4-picoline)	CH,CE (OE) C.B.	CH-OC-H	CB-C(-0) C-B-	1so-pantyl	teo-bucy!	1 may	n-pancy1	TANG-	TAGOZGEN	ethy1	21,21
																																		ř	N. N.
m-F. P-CH30-Ph	3.4-difluoro	5-C1-chipay1-3-y1	thionyl-2-vl	P-CH307C-Ph-		N-methyl-3-pyridinium, I'	3-pyridine	M-mechyl-4-pyridiatum, I'	4-pyridine	m-CHjO-, p-7-Ph-	3, 4, dloxymethylene-9h	mer, p-cajo-an-	٠.	(n.) -cu3- (ccu3cu3) 3-0-	dimethylpiperatine) -	F. B- (N. N-		(8')-613-(0613613) 3-0-	dimechylplperazine) -	I", P-(N, N-	(OCH_CH2) 2-0-Ph-	I", m-(CH3) 3-N"-CH3CH3-		I. b-(CHJ) J-NCHSCHS-	I", m~(CR <sub>3</sub> ) 3-N°-Ph-	I", p-(CB <sub>3</sub> ) 3-W*-Ph-	m-(CH <sub>3</sub> ) 2N-Ph-	P-(CH) 34-Ph-	B-CR30-YA-		P-CH <sub>3</sub> O-Ph-	#-F-971-	P-7-Ph-	100	P.S
continued next page	(-(2)-curopaene	7-13-130-132	J-NULT CHE BE	7-NHC(+O)CH_BE	7-88C(-0)Cgn11		7-(N)-N'-dimethylpiperazinium, I"	7-(N)-N'-methylpiperatine	į	7-[N]-N-methyl-pyrrolidinium, I"	7- (N) -pyrrolidine	7-(N)-N-methylazatidinium, I	7-(N) -ezecidine	7- (N) -morpholine	7-N° (Ma) 2CH2CO2H, I"	7-NNeCE3CO3E	7-8 (CS2CS3) 2	7-NBC (=0) CB3	)=H (CH3) 3, I		J-MRCH3	7-WROK	T-NE2	7-SCH <sub>2</sub> CH <sub>3</sub>	7-50 <sub>7</sub> CH <sub>3</sub>	7-30CH <sub>3</sub>	1-3CH <sub>3</sub>	7-0(1so-propy1)	7-00:85	7-08	7-cerc-bucy1	7-iso-propy1	7-achy1	7-machy1	(R <sup>E</sup> ) q

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8-NHC(O)CH2Br 8-NHC(O)CH2Br 8-NH-C(NH)NH2 )-N-methylazetidinium, I'

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invention comprise a core structure having two or more described above, covalently bonded to the core molety pharmaceutically active benzothiepine structures as via functional linkages. Such active benzothiepine Further preferred compounds of the present structures preferably comprise:

(Formula DIV)

-(H)-N'-machylpiperazina -(H)-N'-dimethylpiperazinium, I - (N) -Pyrrolidine - (N) -N-methyl-pyrrolidinium, I'--B-methylazetidialum, I"

9-NB-CB2 9-NB-C (O) C4B11 9-NHC (O) CB2BT 9-NH-C (NB) MB2 9-(2) -chiophene

(Formula DIVA)

where R', R', R', R', R', R', R', X, q and n are as defined above, and R" is either a covalent bond or arylene.

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S'R'R', PR7, P+R7R8, phenylene, heterocycle, quatarnary or more carbon replaced by O, NR', NR'R', S, SO, SO2, heterocycle, quaternary heteroaryl, or aryl, acid, and peptide polypeptide, can optionally have one polyether diyl, polyalkoxy diyl, carbohydrate, amino alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl acid, and peptide, polypeptide, wherein alkane diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, The core moiety can comprise alkane diyl, alkene

N+R9R11R12A-;  $P(0)R^{13}R^{14}$ ,  $P^{+}R^{13}R^{14}R^{15}A^{-}$ ,  $P(0R^{13})OR^{14}$ ,  $S'R^{12}R^{14}A^{-}$ , and ом, so<sub>2</sub>ом, so<sub>2</sub> $NR^{13}R^{14}$ , c(o) $NR^{13}R^{14}$ , c(o)ом, co $R^{13}$ ,  $\rm SO_2R^{13}$ ,  $\rm SO_3R^{13}$ ,  $\rm NR^{13}OR^{14}$ ,  $\rm NR^{13}NR^{14}R^{15}$ ,  $\rm NO_2$ ,  $\rm CO_2R^{13}$ ,  $\rm CN$ , polyether, aryl, haloalkyl, cycloalkyl, heterocycle, group consisting of alkyl, alkenyl, alkynyl, polyalkyl, arylalkyl, halogen, oxo,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(O)R^{13}$ polyalkoxy diyl, carbohydrate, amino acid, peptide, and polyalkane diyl, alkoxy diyl, polyether diyl, substituent groups independently selected from the polypeptide can be substituted with one or more wherein alkane diyl, alkene diyl, alkyne diyl,

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 $NR^{7}R^{8}$ ,  $SR^{7}$ ,  $S(0)R^{7}$ ,  $S02R^{7}$ ,  $S03R^{7}$ ,  $C02R^{7}$ , CN, OXO, and P(O) (OR') OR', and heterocycle, quaternary heteroaryl, P(0)R<sup>7</sup>R<sup>8</sup>, P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A<sup>-</sup> cycloalkyl, heterocycle, arylalkyl, quaternary  $conr^2 r^8$ ,  $n^+ r^2 r^8 r^9 a^-$ , alkyl, alkenyl, alkynyl, aryl, groups selected from the group consisting of OR', can be further substituted with one or more substituent polyether, aryl, haloalkyl, cycloalkyl, and heterocycle wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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can optionally have one or more carbons replaced by O, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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 $NR^{7}$ ,  $N^{+}R^{7}R^{8}A^{-}$ , s, so, so<sub>2</sub>,  $S^{+}R^{7}A^{-}$ ,  $PR^{7}$ ,  $P(0)R^{7}$ ,  $P^{+}R^{7}R^{8}A^{-}$ , or phenylene. Exemplary core moieties include:

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wherein:

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R<sup>33</sup> is selected from the group consisting of C and

N, and

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R" and R" are independently selected from the group consisting of:

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wherein R", R", R" and R" are independently selected from alkyl, alkenyl, alkylaryl, aryl, arylalkyl, cycloalkyl, heterocycle, and heterocycloalkyl,

A' is a pharmaceutically acceptable anion, and k =1 to 10.

R". In compounds of Formula DIVA, it is preferred that bonded at any of their 6-, 7-, 8-, or 9- positions to Formulae DII and DIII, and R" in Formula DIII can be R" comprises a phenylene moiety bonded at a m- or p-In compounds of Formula DIV, R20, R21, R22 in position thereof to R".

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multiply substituted with more than four pendant active In another embodiment, a core moiety backbone, R", unit, multimers thereof, and multimeric mixtures of the alone or in combination. The number of individual core backbone unit, R", can comprise a single core moiety as discussed herein in Formulas DII and DIII can be discussed above, through multiple functional groups different core moiety units discussed herein, i.e., benzothiepine units, i.e., R", R", R", and R" as within the core moiety backbone. The core moiety

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similar or different pendant active benzothiepine units within a single core moiety backbone unit can be in the range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and moiety backbone units can range from about one to about 100, preferably about one to about 80, more preferably one to about 25. The number of points of attachment of about one to about 50, and even more preferably about points of attachment can include bonds to C, S, O, N, even more preferably about one to about 25. Such or P within any of the groups encompassed by the definition of R".

The preferred structures as outlined above for Formula I. achiral, and the substituents R', R', R', R' and R' poly(exyalkylene) or oligo(oxyalkylene), especially combinations of substituents as discussed above. The 3-carbon on each benzothiepine moiety can be The more preferred benzothiepine moieties comprising R20, R11, R12 and/or R20 conform to the can be selected from the preferred groups and core structures can comprise, for example, poly- or oligo(exyethylene) or poly- or oligo (oxypropylene).

# Dosages, Formulations, and Routes of Administration

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contact of these compounds with their site of action in the body, for example in the ileum of a mammal, e.g., a prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce The ileal bile acid transport inhibitor compounds of the present invention can be administered for the human.

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For the prophylaxis or treatment of the conditions referred to above, the compounds of the present invention can be used as the compound per se.

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Pharmaceutically acceptable salts are particularly suitable for medical applications. because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a

salts, and alkaline earth salts such as magnesium and salts, alkali metal salts such as sodium and potassium and trifluoroacetic acids. The chloride salt is ethanesulfonic, fumaric, gluconic, glycolic, pharmaceutically acceptable acid addition salts of the pharmaceutically acceptable anion or cation. Suitable calcium salts. pharmaceutically acceptable base salts include ammonium particularly preferred for medical purposes. Suitable methanesulfonic, succinic, toluenesulfonic, tartaric, isothionic, lactic, lactobionic, maleic, malic such as acetic, benzenesulfonic, benzoic, citric, nitric, sulfonic, and sulfuric acids, and organic acids compounds of the present invention when possible hydrochloric, hydrobromic, phosphoric, metaphosphoric, include those derived from inorganic acids, such as

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the above list. invention are, of course, also required to be pharmaceutically acceptable and are also selected from The anions of the definition of A in the present

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present, including other compounds of the present be a solid or a liquid, or both, and is preferably not be deleterious to the recipient. The carrier can with the other ingredients of the composition and must course, be acceptable in the sense of being compatible admixing the components. from 0.05% to 95% by weight of the active compound. pharmaceutical composition. The carrier must, of presented with an acceptable carrier in the form of a techniques of pharmacy, consisting essentially of Other pharmacologically active substances can also be composition, for example, a tablet, which can contain invention can be prepared by any of the well known formulated with the compound as a unit-dose invention. The pharmaceutical compositions of the The compounds of the present invention can be

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conventional means available for use in conjunction These compounds can be administered by any z

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compounds or as a combination of therapeutic compounds with pharmaceuticals; either as individual therapeutic The amount of compound which is required to

compound chosen, the use for which it is intended, the depend on a number of factors such as the specific mode of administration, and the clinical condition of achieve the desired biological effect will, of course the recipient.

preferably from about 1 mg to about 50 mg/kg sustained release form effective to obtain desired administered 2 to 6 times per day. Doses can be in proportionate multiple subdoses. Subdoses can be administered to the patient in a single dose, or in 10 mg/kg bodyweight/day. This total daily dose can be bodyweight/day, more preferably from about 3 to about from about 0.3 to about 100 mg/kg bodyweight/day results. In general, a daily dose can be in the range of

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preferably about 1 to about 75 mg of compound, more as tablets or capsules, can contain, for example, from benzothiepine ion derived from the salt. preferably from about 10 to about 50 mg of compound about 0.1 to about 100 mg of benzothiepine compound. weights indicated above refer to the weight of the In the case of pharmaceutically acceptable salts, the Orally administrable unit dose formulations, such

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capsule, retention in the stomach based on the physical of the small intestine, slow erosion of a tablet or release from the dosage form based on the changing pH These include, but are not limited to, pH sensitive gastrointestinal tract by any number of mechanisms. prolonged or sustained delivery of the drug to the inhibitor of the present invention can include dosage form to the mucosal lining of the intestinal properties of the formulation, bioadhesion of the formulations, as are well known in the art, to provide dosage form. The intended effect is to extend the time tract, or enzymatic release of the active drug from the Oral delivery of an ileal bile acid transport

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period over which the active drug molecule is delivered to the site of action (the ileum) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate,

nydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid nethyl ester.

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when administered intravenously, the dose can, for example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight to about 0.75 mg/kg body weight, more preferably from about 0.4 mg/kg body weight to about 0.6 mg/kg body weight. This dose can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 mg present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

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Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

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Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one

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general, the compositions are prepared by uniformly and suitable machine, the powdered compound moistened with agent(s). Molded tablets can be made by molding, in a or finely divided solid carrier, or both, and then, if hecessary, shaping the product. For example, a tablet or non-aqueous liquid; or as an oil-in-water or watercan be prepared by compressing or molding a powder or granules of the compound, optionally with one or more granules; as a solution or a suspension in an aqueous intimately admixing the active compound with a liquid in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which compound in a free-flowing form, such as a powder or prepared by compressing, in a suitable machine, the granules optionally mixed with a binder, lubricant, includes the step of bringing into association the constitute one or more accessory ingredients). In compound of the present invention; as a powder or assessory ingredients. Compressed tablets can be inert diluent and/or surface active/dispersing active compound(s) and the carrier (which can an inert liquid diluent.

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Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

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Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravencusly, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood.

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Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

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Pharmaceutical compositions suitable for transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

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In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

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The solid dosage forms for oral administration including capsules, tablets, pills, powders, and

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granules noted above comprise one or more compounds of the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. Liquid dosage forms for oral administration can

include pharmaceutically acceptable emulsions, suspensions, syrups, and elixirs containing solutions, suspensions, syrups, and elixirs containing finert diluents commonly used in the art, such as water Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

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are water, Ringer's solution, and isotonic sodium acceptable vehicles and solvents that may be employed sterile injectable solution or suspension in a nontoxic dispersing or setting agents and suspending agents. addition, fatty acids such as oleic acid find use in employed including synthetic mono- or diglycerides. are conventionally employed as a solvent or suspending chloride solution. example, as a solution in 1,3-butanediol. Among the parenterally acceptable diluent or solvent, for The sterile injectable preparation may also be a formulated according to the known art using suitable the preparation of injectables. medium. injectable aqueous or oleaginous suspensions may be Injectable preparations, for example, sterile For this purpose any bland fixed oil may be In addition, sterile, fixed oils

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Pharmaceutically acceptable carriers encompass all the foregoing and the like.

## Treatment Rogimen

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The dosage regimen to prevent, give relief from, or ameliorate a disease condition having hyperlipemia as an element of the disease, e.g., atherosclerosis, or

the type, age, weight, sex, diet, and medical condition employed may vary widely and therefore deviate from the of the patient, the severity of the disease, the route of administration, pharmacological considerations such and whether the compound is administered as part of a employed, whether a drug delivery system is utilized, compositions of the present invention is selected in accordance with a variety of factors. These include to protect against or treat further high cholesterol drug combination. Thus, the dosage regimen actually plasma or blood levels with the compounds and/or as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound preferred dosage regimen set forth above.

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effective amounts of compounds of the present invention satisfactory effectiveness is administered, and so that levels by any of the methods well known in the art, to are administered at any point in time, and so that the monitored by, for example, measuring serum cholesterol this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that continued as necessary over a period of several weeks Initial treatment of a patient suffering from a duration of treatment can be determined as well. In disease condition has been controlled or eliminated. hyperlipidemic condition can begin with the dosages to several months or years until the hyperlipidemic Patients undergoing treatment with the compounds or determine the effectiveness of therapy. Continuous necessary to successfully treat the hyperlipidemic analysis of such data permits modification of the inhibitor of the present invention which exhibits treatment regimen during therapy so that optimal indicated above. Treatment should generally be compositions disclosed herein can be routinely administration is continued only so long as is the lowest amount of ileal bile acid transport

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illustrate various aspects of the present invention; The following non-limiting examples serve to

EXAMPLES OF SYNTHETIC PROCEDURES

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2-Ethyl-2-(mesyloxymethyl)hexanal (1)

while maintaining the reaction temperature below 30 °C. dried over MgSO, and concentrated in vacuo to give 24.4 methlyene chloride. The methylene chloride extract was for 18 h, quenched with dilute HCl and extracted with triethylamine was added dropwise 15.8 g of 2-ethyl-2procedure described in Chem. Ber. 98, 728-734 (1965), The reaction mixture was stirred at room temperature To a cold (10 °C) solution of 12.6 g (0.11 mole) of methanesulfonyl chloride and 10.3 g (0.13 mole) of (hydroxymethyl)hexanal, prepared according to the

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Preparation 2

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g of brown oil.

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ි න reaction mixture was poured into 3N HCl and extracted procedure described in WO 93/16055, 24.4 g (0.1 mole) nethoxyethyl ether was held at reflux for 24 h. The of 2-ethyl-2-(mesyloxymethyl)-hexanal (1), 14.8 g 2-((2-Benzoylphenylthio)methyl)-2-ethylbexanal (2) mercaptobenzophenone, prepared according to the (0.146 mole) of triethylamine, and 80 mL of 2-A mixture of 31 g (0.144 mol) of 2-

methoxyethyl ether. The residue was purified by HPLC dried over MgSO, and concentrated in vacuo to remove 2chloride layer was washed with 300 mL of 10% NaOH, with 300 mL of methylene chloride. The methylene (10% EtOAc-hexane) to give 20.5 g (58%) of 2 as an oil

dihydro-benzothiepin-(5H)4-one (4b) cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine (3), (5H)4-one (4a) and trans-3-Butyl-3-ethyl-5-phenyl-2,3-

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methylene chloride. The methylene chloride extract was the earlier fraction and  $0.1~\mathrm{g}$  (3%) of 4b in the later purified by HPLC (hexane) to give 0.07 g (2%) of 4m in was discarded and the third fraction was further as an oil in the first fraction. The second fraction was purified by HPLC (hexane) to give 1.7 g (43%) of 3 dried over MgSO, and concentrated in vacuo. The residue being poured into brine. The organic was extract into h and then was held at reflux for 2 h and cooled before reaction mixture was stirred at room temperature for 16 g (0.01 mole) of 2 in 30 mL of DME in 40 min. The reaction mixture was added dropwise a solution of 3.54 glycol dimethyl ether (DME) was held at reflux for 2 h. A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g 4, The reaction mixture was cooled to 5 °C. To the (0.047 mole) of TiCl, and 80 mL of anhydrous ethylene

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#### Example 2

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<u>SP</u> t phenyl-2,3-dihydro-benzothiepin-(5H)4-one-1,1-dioxide(5H)4-one-1,1-dioxide (5a) and trans-3-Butyl-3-ethyl-5cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-

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20 mL of methylene chloride was added 0.59 g (1.75 To a solution of 1.2 g (3.5 mmode) of 50-60% MCPBA in 54,56

> WO 97/33882 chloride. The reaction mixture was stirred for 20 h., An mmole) of a mixture of 4a and 4b in 10 mL of methylene was purified by HPLC (5% EtOAc-hexane) to give 0.2 g MgSO, and concentrated in vacuo. The residual syrup insoluble solid was filtered. The methylene chloride 3 h then was triturated with 50 mL of 10% NaOH. The and the reaction mixture was stirred for an additional additional 1.2 g (1.75 mmole) of 50-60% MAPBA was added (30%) of 5m as an oil in the first fraction and 0.17 g layer of the filtrate was washed with brine, dried over (26%) of 5b as an oil in the second fraction.

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothicai-- ' ' ' benzothiepine-1,1-dioxide (6b), (3a,4a,5a) 3-Butyl-3tetrahydrobenzothiepine-1,1-dioxide (6a), (3a,4b,5a) 3-A. Reduction of 5a and 5b with Sodium Borohydride Buty1-3-ethy1-4-hydroxy-5-pheny1-2,3,4,5-tetrahydrotetrahydrobenzothiepine-1,1-dioxide (6d) sthy1-4-hydroxy-5-pheny1-2,3,4,5-(3a,4a,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4 Example 3 9 (49) NOW (33)

To a solution of 0.22 g (0.59 mmole) of 5b in 10 mL of and extracted with methylene chloride. The methylene remove ethanol. The residue was triturated with water temperature for 18 h and concentrated in vacuo to borohydride. The reaction mixture was stirred at room ethanol was added 0.24 g (6.4 mmole) of sodium g (27%) of 6a as a syrup. The second fraction was 0.2~gup as described above to give 0.5 g of syrup which was sodium borohydride in 10 mL of ethanol and was worked experiment, 0.45 g of 5a was treated with 0.44 g of chloride extract was dried over MgSO, and concentrated 10% EtOAc-hexane as eluant. The first fraction was 0.18 two materials were combined and purified by HPLC using identical to the 0.2 g of syrup obtained above: These in vacuo to give 0.2 g of syrup. In a separate

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(30%) of 6b also as a syrup. The column was then eluted hexane gave a solid, mp 179-181 °C. Finally, the column Recrystallization from hexane gave a solid, mp 160-161 the third fraction as a solid. Recrystallization from was eluted with 30% EtOAc-hexane to give 0.08 g (12%) with 20% BtOAc-hexane to give 0.077 g (11%) of 6d in of 6d in the fourth fraction as a solid.

# B. Conversion of 6a to 6c and 6d with NaOH and Prc

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was stirred for 0.5 h at room temperature and was added CH,Cl, , was added 9 g of 40% NaOH. The reaction mixture components of this mixture were separated using an HPLC and eluted with EtOAc-hexane to give 12.8 mg (4%) of 2fraction and 90.0 mg (31%) of 6d in the third fraction. was stirred for 0.5 h at room temperature before being with CH,Cl, (3x10 ml), dried over MgSO, and concentrated treated with 25 mL of ice-crystals then was extracted chloride) phase transfer catalyst (PTC). The mixture (2-benzylphenylsulfonylmethyl)-2-ethylhexenal in the To a solution of 0.29 g (0.78 mmole) of 6a in 10 mL in vacuo to recover 0.17 g of a colorless film. The one drop of Aliquat-336 (methyltricaprylylammonium first fraction, 30.9 mg (11%) of 6c in the second

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## Oxidation of 6a to 5b

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h then was treated with additional 0.23 g of pyridinium chlorochromate and stirred overnight. The dark reaction mixture was poured into a ceramic filterfrit containing chlorochromate. The reaction mixture was stirred for 2 silica gel and was eluted with CH,Cl,. The filtrate was concentrated in vacuo to recover 167 mg (87%) of 5b as To a solution of 0.20 g (0.52 mmole) of 6a in 5 mL of CH,Cl, was added 0.23 g (1.0 mmole) of pyridinium a colorless oil.

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Example 4

3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobonzothiepine-1,1-Q 1/2/2 dioxido (7)

criturated with 25 mL of water followed by 50 mL of 10% mixture was allowed to stir overnight under N, and was To a solution of 5.13 g (15.9 mmole) of 3 in 50 mL of (4x20 mL). The CH,Cl, extract was dried over MgSO, and chloroperoxybenzoic acid) portionwise causing a mild CH,Cl, was added 10 g (31.9 mmole) of 50-60% MCPBA (mreflux and formation of a white solid. The reaction WaOH solution. The organic was extracted into CH,Cl, evaporated to dryness to recover 4.9 g (87%) of an opaque viscous oil.

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totrahydro-banzothispino[4,5-b]oxirono-4,4-dioxido (8a) totrahydro-benzothiepino [4,5-b]oxirono-4,4-dioxide (laa, 2b, 8ba ) 2-Butyl-2-othyl-8b-phenyl-1a, 2, 3, 8b-[laa, 2a, 8ba] 2-Butyl-2-othyl-8b-phomyl-la, 2, 3, 8b-

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portionwise 5 g (14.1 mmole) of 50-60 % MCPBA causing a with brine, dried over MgSO,, and concentrated in vacuo extracted with 10% potassium carbonate (3x50 mL), once crystalline product in hexane recovered 141.7 mg (10%) mild exotherm. The reaction mixture was stirred under insoluble white slurry was filtered. The filtrate was to give 1.37 g of a light yellow oil. Purification by HPLC gave 0.65 g of crystalline product. This product To 1.3 9 (4.03 mole) of 3 in 25 mL of CHC1, was added N, overnight and was then held at reflux for 3 h. The concentrated in vacuo to give 206 mg of white film which is a mixture of 30% 8a and 70% 8b by 'H NMR. is a mixture of two isomers. Trituration of this of a white crystalline product. This isomer was (laa, 2b, 8ba) isomer 8a. The hexane filtrate was characterized by NMR and mass spectra to be the 15 402) Jan (8a) Ó

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Thenyl-2.3% 5-tetrahydro-

cis-3-Butyl-3-ethyl-5-phenyl-2,3%,5-tetrahydro- ()
benzothiepine-1,1-dioxide (9a), trans-3-Butyl-3-ethyl5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide
(9b), and 3-Butyl-3-ethyl-4-hydroxy-5-cyclobexylidine2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (10)

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(5%) of a mixture of 6d and one of the isomers of 10, based on mass spectrum. The sixth fraction was 7.5 mg phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide product believed to be 3-butyl-3-ethyl-4,5-dihydroxy-5fraction was 9.6 mg (7%) of a mixture of 6b and a and 9b. The third fraction was 8.8 mg (6%) of 6a . The second fraction, 5.0 mg (4%), was a 50/50 mixture of 98 hexane. The first fraction was 4.2 mg (3%) of 9b. The This material was purified by HPLC eluting with EtOAcdryness in vacuo to recover 0.117 g of a colorless oil catalyst. This mixture was hydrogenated at 70 psi H Fisher/Porter vessel, then was added 0.1 g of 10% Pd/C A mixture of 0.15 g (0.4 mmole) of a 3:7 mixture of 8a fourth fraction was 25.5 mg (18%) of 6b. The fifth for 5 h and filtered. The filtrate was evaporated to and 8b was dissolved in 15 ml MeOH in a 3 oz.

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#### Example 7

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In another experiment, a product (3.7 g) from epoxidation of 3 with excess MCPBA in refluxing CHCl, under air was hydrogenated in 100 mL of methanol using 1 g of 10% Pd/C catalyst and 70 psi hydrogen. The product was purified by HPLC to give 0.9 g (25%) of 9b 0.45 g (13%) of 9a, 0.27 g (7%) of 6a, 0.51 g (14%) of 6b, 0.02 g (1%) of 6c, 0.06 g (2%) of one isomer of 10 10a and 0.03 g (1%) of another isomer of 10, 10b.

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Example 8

2-((2-Benzoylphenylthio)methyl)butyraldehyde (11)

of 2-ethylacrolein in 40 mL of dry THF was added 24.6 g washed with 50 mL of 1 M potassium carbonate three by kugelrohr distillation at 0.5 torr (160-190 °C) gave The ether layer was dried over MgSO, and concentrated with dilute HCl, brine, and 1 M potassium carbonate. To an ice bath cooled solution of 9.76 g (0.116 mole) times to give 6.0 g of a syrup which was purified by a fraction (12.2 g) which contained starting material in vacuo. The residue was purified by HPLC (10% EtOAcreaction mixture was stirred at room temperature for 3 followed by 13 g (0.128 mole) of triethylamine. The HPLC (10% EtOAc-hexane) to give 5.6 g of pure 11 This material was dissolved in ether (100 mL) and was indicating a reversed reaction during distillation. fraction. An attempt to further purifiy this material hexane) to give 22 g (64%) of 11 in the second days , diluted with ether, and was washed successively (0.116 mole) of 2-mercaptobenzophenone in 40 mL of THF

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Example 9

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3-Ethyl-5-phenyl-2,3-dihydrobenzothiepine (12)

To a mixture of 2.61 g (0.04 mole) of zinc dust and 60 mL of DME was added 7.5 g (0.048 mole) of TiCl, The reaction mixture was held at reflux for 2 h. A solution of 2.98 g (0.01 mole) of 11 was added dropwise in 1 h. The reaction mixture was held at reflux for 18 h, cooled and poured into water. The organic was extracted into ether. The ether layer was washed with brine and filtered through Celite. The filtrate was dried over MgSO, and concentrated. The residual oil (2.5 g) was purified by HPLC to give 2.06 g (77%) of 12 as an oil in the second fraction.

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Example 10 (3) (3) (1aa, 2a, 8ba) 2-Ethyl-8b-phenyl-1a, 2, 3, 8b-tetrahydrobenzothiepino-[4,5-b]oxirene-4,4-dioxide (13)

Portionwise causing an exothem and formation of a white To a solution of 1.5 g (5.64 mmole) of 12 in 25 ml of recover 1.47 g of an off white solid. 'H NMR indicated 0.82 g (46%) of 13 as a white solid, mp 185-186.5 °C. overnight diluted with 100 ml methylene chloride and slurried in 200 ml of warm Et,O and filtered to give twice with 25 ml) and brine. The organic layer was solid. The mixture was stirred at room temperature washed successively with 10% K,CO, (4x50 ml), water then dried over MgSO, and evaporated to dryness to CHCl, was added 6.8 g (19.4 mmole) of 50-60% MCPB that only one isomer is present. This solid was

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tetrahydro-benzothiepine-1,1-dioxide (14a), (3a,4b,5b) tetrahydrobenzothiepine-1,1-dioxide (14b), and cis-3-Ethyl-5-phenyl-2,3,4,5-tetrahydro-benrothlepine-1,1-(3a,4b,5a)- 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-3-Ethyl-4-bydroxy-5-phenyl-2, 3, 4, 5-

with 70 psi hydrogen for 4 h. The crude reaction slurry (87%) of a voluminous white solid which was purified by first fraction, 272 mg (54%) of 16a as a solid, mp 142-HPLC (EtOAc-Hexane) to give 26.8 mg (6%) of 15 in the dioxide (15) 0.5% et 0.5% (4c) 6.5% (4c) 0.5% (4c) 0.5% (4c) 0.5% (1.6 mole) of 13, 50 ml of acetic was filtered and the filtrate was stirred with 150 ml acetic acid. The mixture was extracted with methylene acid and 0.5 g of 10% Pd/C catalyst was hydrogenated chloride (4x25 ml), then the organic layer was dried over MgSO, and concentrated in vacuo to give 0.44 g NaHCO, powder portionwise to neutralize the rest of of a saturated NaHCO, solution followed by 89 g of

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143.5 °C, in the second fraction, and 35 mg (7%) of impure 14b in the third fraction.

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2-Ethyl-2-((2-Rydroxymethylphenyl)thicmethyl)hexenal

alcohol, 6.4 g (0.032 mole) of 1, 3.6 g (0.036 mole) of at reflux for additional 16 h. The reaction mixture was mercaptobenzyl alcohol and 0.72 g of triethylamine was added to the reaction mixture and the mixture was held methylene chloride. The methylene chloride extract was A mixture of 5.0 g (0.036 mole) of 2-mercaptobenzyl triethylamine and 25 mL of 2-methoxyethyl ether was Purification by HPLC (20% EtOAc-hexane) gave 3.7 g cooled and poured into 6N HCl and extracted with washed twice with 10% NaOH, dried over MgSO, and concentrated in vacuo to give 9.6 g of residue. held at reflux for 7 h. Additional 1.1 g of (41%) of 16 as an oil.

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## Example 13

2-Ethyl-2-((2-formylphenyl)thiomethyl)hexenal (17) Q X (1)

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chloride eluant was purified by HPLC (20% ETOAc-hexane) through a bed of silica gel. The silica gel was eluted pyridinium chlorochromate, 2 g of Celite and 30 mL of methylene chloride was stirred for 18 h and filtered A mixture of 3.7 g of 16, 5.6 g (0.026 mole) of with methylene chloride. The combined methylene to give 2.4 g (66%) of an oil.

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(E) 3-Butyl-3-ethyl-2, 3-dihydrobenzothiepine (18)

(0.047 mole) of TiCl,, and 50 mL of DME was held at A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g

a residue. Purification by HPLC gave 0.41 g (20%) of 18 over MgSO, and concentrated in vacuo to give 3.0 g of chloride-water mixture was filtered through Celite. The stirred with methylene chloride. The methylene as an oil in the early fraction. methylene chloride layer was washed with brine, dried reaction mixture was poured into dilute HCl and was DME in 10 min. The reaction mixture was stirred at room mixture was added 2.4 g (8.6 mmole) of 17 in 20 mL of let standing at room temperature over weekend. The temperature for 2 h and held at reflux for 1 h then was reflux for 2 h and cooled to room temperature. To this

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tetrahydro-bonzothiepino[6,5-b]oxirene-4,4-dioxide (1ac, 2b, 8ba) 2-Butyl-2-othyl-8b-phenyl-1a, 2, 3, 8bbenzethiepino(4,5-b)exirene-4,4-diexide (19a) and (laa,2a,8ba ) 2-Butyl-2-ethyl-la,2,3,8b-totrahydro-CO SOLL PAR 18 John 19 Joh

0.12 g of syrup in the first fraction. mp 89.5-105.5 °C. The mother liquor from the first Recrystallization from hexane gave 0.08 g (17%) of 19a concentrated in vacuo. The residue was purified by HPLC NaOH and 5 g of sodium sulfite. The methylene chloride The reaction mixture was stirred with 100 mL of 10% 30 mL of CHCl, and was held at reflux for 18 h under  $N_1$ . and concentrated in vacuo. The residue was dissolved in 50-60% MCPBA. The reaction mixture was stirred for 2 h mL of methylene chloride was added 2.2 g (3.2 mmole) of To a solution of 0.4 g of 0.4 g (1.6 mmole) of 18 in 30 further purified by HPLC (10% EtOAc-hexane) to give (20% EtOAc-hexane) to give a third fraction which was layer was washed with brine, dried over MgSO, and

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first fraction and 60 mg of 19b in the second fraction further purified by HPLC to give additional 19a in the fraction was combined with the second fraction and was

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Crystallization from hexane gave 56 mg of a white

3-Buty1-3-othy1-4,5-d1hydroxy-5-pheny1-2,3,4,5 tetrahydro-benzothiepine-1,1-dioxide (20)

#### Example 17

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3-Butyl-3-ethyl-4-hydroxy-5-phonylthio-2,3,4,5tetrahydro-benzothiepine-1,1-dioxide (21)

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second fraction and 11 mg of a third fraction which hexane to give 17 mg of a first fraction, 4 mg of a and concentrated in vacuo to give 0.19 g of semisolid A mixture of 25 mg (0.085 mmole) of 19b, 0.27 g (2.7 21c, respectively, by 'H NMR and mass spectra. EtOAc-hexane) to remove diphenyl disulfide in the first disulfide. This material was purified by HPLC (5% successively with 10% NaOH and brine, dried over MgSO, chloride. The methylene chloride layer was washed carbonate, and 4 mL of DMF was stirred at room mmole) of thiophenol, 0.37 g (2.7 mmole) of potassium were three different isomers of 21, i.e. 21a, 21b, and fraction. The column was then eluted with 20% EtOAcwhich contain substantial amounts of diphenyl poured into water and extracted with methylene temperature under N, for 19 h. The reaction mixture was

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### Example 18

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Altornative Synthesis of 6c and 6d

ethylhoxanal (2) A. Preparation from 2-((2-Benzoylphenylthio)methyl)-2-

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ethylhexanal (66) Stop 1. 2-((2-Benzoylphenylsulfonyl)mothyl)-2

carbonate, once with 10% sodium hydroxide and once with mol) of 50-60% MCPBA portionwise. The reaction mixture filtered through Celite. The methylene chloride layer chloride solution was dried and concentrated in vacuo to give 9.2 g (95%) of semisolid. A portion (2.6 g) of To a solution of 9.0 g (0.025 mole) of compound 2 in 100 ml of methylene chloride was added 14.6 g (0.025 brine. The insoluble solid formed during washing was removed by filtration through Celite. The methylene stirred with 200 ml of 1 M potassium carbonate and this solid was purified by HPLC(10% ethyl acetatewas stirred at room temperature for 64 h then was nexane) to give 1.9 g of crystals, mp 135-136 °C was washed twice with 300 ml of 1 M potassium

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Step 2. 2-((2-Bensylphenylculfonyl)methyl)-2-othylhexanal (45)

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A solution of 50 g (0.13 mole) of crude 66 in 250 ml of was charged 125 ml of methanol and 5 g of 10% Pd/C. The repeated one more time but only 1 g of Pd/C was charged for 7 h before being charged with an additional 5 g of to the reaction mixture. The combined reaction mixture charged to two Fisher-Porter bottles. To each bottle was filtered and concentrated in vacuo to give 46.8 g 10% Pd/C. The reaction mixture was again hydrogenated bottles were pressurized with 70 psi of hydrogen and the reaction mixture was stirred at room temperature with 70 psi of hydrogen for 7 h. This procedure was methylene chloride was divided in two portions and of 45 as brown oil.

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Step 3. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phonyl-[3a, 4b, 5b] 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-2,3,4,5-totrahydrobenzothiepine-1,1-dioxide (6c), and totrahydrobensothiepine-1,1-dioxide (6d)

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To a solution of 27.3 g (73.4 mmole) of 45 in 300 ml of anhydrous THF cooled to 2 °C with an ice bath was added reaction mixture was stirred for 20 min, quenched with chloride. The methylene chloride layer was dried over fraction and 6.5 g (24%) of 6d in the third fraction. acetate-hexane) yielded 9.4 g of recovered 45 in the 9.7 g (73.4 mmole) of 95% potassium t-butoxide. The magnesium sulfate and concentrated in vacuo to give 24.7 g of yellow oil. Purification by HPLC (ethyl first fraction, 5.5 g (20%) of 6c in the second 300 ml of 10% HCl and extracted with methylene

B. Preparation from 2-hydroxydiphenylmothane Step 1. 2-marcaptodiphenylmethane (46)

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sodium hydride oil dispersion. The sodium hydride was To a 500 ml flask was charged 16 g (0.33 mol) of 60% flask was charged 100 ml of DMF. To this mixture was washed twice with 50 ml of hexane. To the reaction

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mixture was stirred at room temperature for 30 min then h before being poured into 300 ml of water. The organic orine and was concentrated in vacuo to give 78.6 g of a reaction mixture was stirred at room temperature for 18 was extracted into 500 ml of toluene. The toluene layer yellow oil which was 95% pure dimethyl 0-2-benzylphenyl The distillate (56.3 g) was crystallized from methanol temperature was maintained below 30 °C by an ice-water was washed successively with 10% sodium hydroxide and thiocarbamate. This oil was heated at 280-300 °C in a residue was kugelrohr distilled at 1 torr (180-280 °C) cooled with an ice bath. To the reaction mixture was hydroxydiphenylmethane in 200 ml of DMF in 1 h while chloride at once. The ice bath was removed and the added 49.4 g (0.4 mole) of dimethyl thiocarbamoyl bath. After complete addition of the reagent, the tugelrohhr pot under house vacuum for 30 min. The added a solution of 55.2 g (0.3 mol) of 2-

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to give 37.3 g (46%) of the rearranged product dimethyl

mercaptodiphenylmethane as a yellow solid. crystallized from hexane to give 37.1 g (88%) of 2sulfate and concentrated in vacuo. The residue was mixture of 57 g (0.21 mole) of this yellow solid, 30 gether. The ether extract was dried over magnesium concentrate HCl, The oily suspension was extracted into with ether. The agueous layer was made acidic with residue was diluted with 200 ml of water and extracted stirred overnight then was concentrated in vacuo. The of potassium hydroxide and 150 ml of methanol was S-2-benzylphenyl thiocarbamate as a yellow solid. A

## (2) Step 2. 2-((2-Benzylphenylthio)methyl)-2-othylhoxanal 36,

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ethylhexanal 67 as a yellow syrup. eluent to give 2-((2-benzylphenylthio)methyl)-2was purified by HPIC with 2-5% ethyl acetate-hexane as sulfate and concentrated in vacuo. The residue (98.3 g) organic was extracted into 400 ml of ether. The ether 500 ml of water and 30 ml of concentrate HCl. The concentrated in vacuo. The residue was triturated with A mixture of 60 g (03 mole) of yellow solid from step hydroxide and brine and was dried over magnesium methoxyethyl ether was held at reflux for 6 hr and 32.4 g (0.32 mole) of triethylamine, 120 ml of 2-1, 70 g (0.3 mole) of compound 1 from preparation 1, layer was washed successively with brine, 10% sodium

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## ethylhoxonal (65) Step 3. 2-((2-Benzylphanylsulfonyl)methyl)-

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g of 50-60% MCPBA was added to the reaction mixture. reaction mixture was stirred for 2 h. An additional 13 The reaction mixture was stirred for 2 h and filtered 10 °C was added 132 g of 50-60% MCPBA in 40 min. The from step 2 in 1 liter of methylene chloride cooled to To a solution of 72.8 g (0.21 mole) of yellow syrup (45)

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washed twice with 1 liter of 1 M potassium carbonate ethylhexanal 45 as a syrup to 76 g of 2-{(2-benzylphenylsulfonyl)methyl)-2layer was dried over magnesium sulfate and concentrated then with 1 liter of brine. The methylene chloride through Celite. The methylene chloride solution was

2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and Step 4. (3a, 4a, 5a) 3-Butyl-3-ethyl-4-hydroxy-5-phonyltetrahydrobenzothiepine-1,1-dioxide (6d) (3a, 6b, 5b) 3-Butyl-3-ethyl-4-hydroxy-5-phonyl-2,3,6,5-

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the procedure in step 3 of procedure A gave pure 6c and 6d after HPLC. 3  $\xrightarrow{E^t}$  8. Reaction of 45 with potassium t-butoxide according to

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Example 19

(22)

phenylthio)methyl)-2-ethylhexanal (22) Stap 1. Preparation of 2-((2-benzoyl-4-methomy phenyl-2,3,6,5-totrahydrobenzothiepine-1,1-dioxido (26) phonyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (25) and (3a, &a, 5a) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-(3a, 6b, 5b) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-

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needed. The thermal rearrangement was performed by previously described in example 18. The product can be dimethyl 0-2-benzoyphenyl thiocarbamate by methods 2-Hydroxy-4-methoxybenzophenone was converted to the described below procedure which avoided a chromatography step was 260 °C as previously described. The improved isolation reacting the thiocarbamate (5 g) in diphenyl ether at improved isolation procedure no chromatography was isolated by recrystallization from ethanol. Using this

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3.5 g of KOH for 4 h. After removing THF and methanol 100 ml of methanol and 100 ml of THF in the presence of The crude pyrolysis product was then heated at 65 °C in

by rotary evaporation the solution was extracted with 5 KOH. After acidification and extraction with ether pure thiophenol product. The product was further purified by titrating the desired mercaptan into base with limited 2-mercapto-4-methoxybenzophenone (2.3 g) was isolated. & NaOH and ether. The base layer was acidified and extracted with ether to obtain a 2.9 g of crude

reaction with 2-ethyl-2-(mesyloxymethyl)hexanal (1) as methoxyphenylthio)methyl)-2-ethylhexanal (22) by 2-mercapto-4-methoxybenzophenone can readily be converted to the 2-((2-benzoyl-4previously described.

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Stop 2. 2-((2-Benzoyl-5-methoxyphenylsulfonyl)methyl)-(23) \*\*\*- 5回のf 2-othylbexenal (23)

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Substrate 22 was readily oxidized to 2-((2-bonzoyl-5methoxyphonyl-sulfonyl)methyl)-2-ethylhemanal (23) as described in example 18. House 50-c4 18. (24)

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Stop 3. 2-((2-banzyl-5-mothoxyphenylsulfonyl)methyl)-2othylhemnnal (24)

methoxyphonyl-sulfonyl)methyl)-2-ethylhexanal (24) as 4; 00 30 1 4 (215) Sulfone 23 was then reduced to 2-((2-bonzyl-5described in example 18.

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(E) Gtep 4. (3a, 4b, 5b) 3-Butyl-3-ethyl-4-hydroxy-8-methoxymethoxy-5-phonyl-2,3,4,5-tetrahydrobenzothiepins-1,1-5-phenyl-2,3,4,5-tetrabydrobenzothiopins-1,1-dioxide 1.05 Tely 5,1 (25) and (3a, 4a, 5a) 3-Butyl-3-othyl-4-hydroxy-8-HoxIde (26)

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funnel, thermocouple and nitrogen bubbler was charged with 19.8 g (0.05 mole) of sulfone 24 in 100 ml dry A 3-neck flask equipped with a powder addition 4 THF. The reaction was cooled to -1.6 °C internal

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indicated a 96% conversion to a 50/50 mixture of 25 and temperature by means of ice/salt bath. Slowly add 5.61 The only other observable compound was 4% starting g (0.05 mole) of potassium t-butoxide by means of the layer was extracted with 300 ml of methylene chloride. dryness to obtain 19.9 g of product. 'H nmr and glpc solution was extracted with cold 10 % HCl. The acid powder addition funnel. The resulting light yellow magnesium sulfate and after filtration stripped to solution was maintained at -1.6 °C. After 30 min reaction 400 ml of cold ether was added and this the organic layers were combined and dried over sulfone 26.

was allowed to cool to room temperature and in this way hexane/ethyl acetate by warming to 50 °C. The solution crystallizations the mother liquor which was now 85.4% enhanced by addition of a seed crystal of 26. After 2 dissolved in 100 ml of 90/10 hexane/ethyl acetate and isolated by seeding this solution with a seed crystal pure 26 can be isolated. The crystallization can be 25 and has a dry weight of 8.7 g. This material was 10 ml of pure ethyl acetate at 40 C. Pure 25 can be The product was then dissolved in 250 ml of 90/10 of 25 after storing it overnight at 0 C.

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Example 20

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(3a,4a,5a) 3-Butyl-3-athyl-6,8-dihydroxy-5-phonyl-2, 3, 4, 5-tetrohydrobenzothiepine-1, 1-dioxido (27)

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In a 25 ml round bottomed flask, 1 g of 26( 2.5 mmoles) to slowly warm to room temperature and stirred for 6 h. mmole) was added via syringe. The reaction was allowed and 10 ml methylene chloride were cooled to - 78 °C with stirring. Next 0.7 ml of boron tribromide(7.5 The reaction was then diluted with 50 ml methylene chloride and washed with saturated NaCl and then water. The organic layer was dried over magnesium

NMR and mass spectra sulfate. The product (0.88g) 27 was characterized by

### Example 21

General Alkylation of phenol 27

the ethoxylated product 28 was obtained in high yield ml) and then sat. NaCl. After stripping off the solvent equivalent of the alkyl halide was used. For higher boiling alkyl iodides and bromides only one in table 1 from the corresponding iodides or bromides. This same procedure was used to prepare products listed The product was characterized by NMR and mass spectra. ether and washed with water (25 ml) then 5% NaOH (20 overnight. The reaction was diluted with 50 ml ethyl mmole). The reaction was stirred at room temperature carbonate(0.38 mmole) and 140 mg ethyl iodide (0.9 mmole), 5 ml anhydrous DMF, 54 mg of potassium A 25 ml flask was charged with 0.15 g of 27(0.38

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Table 1

Compound No. hexyl 띥 ĕ (CH2) 6-N-pthalimide

Example 22

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phonyl-2,3,4,5-tetrahydrobenzothicpino-1,1-dioxido (37) and (3a, 4b, 5b) 3-Butyl-3-ethyl-4-hydroxy-7-(3a, da, 5a) 3-Butyl-3-ethyl-d-hydroxy-7-hydroxyamino-5-

hydroxyamino-5-phonyl-2,3,4,5-tetrahydrobonzothiepine-1,1-dioxido (38)

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(32) Step 1. Preparation of 2-chloro-5-nitrodiphenylmethane (35) (9)

9 770-772 (1986) Olah G. Et al Procedure adapted from reference : Synthesis -Stuttgart

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acid in 345 ml methylene chloride was added slowly. Under nitrogen, a 3 neck flask was charged with 45 g the additions were completed the reaction was allowed sulfonic acid and triethylsilane) were repeated. After solution. Both addition steps (trifluoromethane Next 30 g of triethylsilane (0.172 mole) in 345 ml methylene chloride and the solution was cooled to layers. The methylene chloride layer was isolated and Poured into a 4 liter separatory funnel and separated saturated sodium bicarbonate. Gas evolution occurred poured into a chilled stirred solution of 1600 ml of 12 h under nitrogen. The reaction mixture was then to slowly warm up to room temperature and stirred for methylene chloride was added dropwise to the chilled funnel, 150 g( 0.172 mole) of trifluoromethane sulfonic ice/water temperature. By means of an additional (0.172 mole ) of 2-chloro-5-nitrobenzophenone in 345 ml

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combined with two 500 ml methylene chloride extractions of the aqueous layer. The methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from hexane to give 39 g product. Structure 32 was confirmed by mass spectra and proton and carbon NMR.

Step 2. Preparation of 2-((2-benzyl-4-
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)  $\stackrel{=}{\sim}$  nitrophonylthio)mathyl)-2-ethylhaxanal (33)  $\stackrel{(33)}{\sim}$   $(33)$ 

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flask with water condenser. Next 150 ml DMSO and 7.18 g stirring, extracted with 4 X 700 ml of ether, and dried Next the reaction mixture was slowly poured mixture was heated to 80 °C under nitrogen. After 12 0.156 mole) from above was placed in a 2 liter 2 neck The 2-chloro-5-nitrodiphenylmethane product 32 (40 g, monitored by TLC and added more mysylate if necessary over MgSO4. After removal of ether, 82.7 g of product as isolated. The material can be further purified by thyl acetate. If pure mysylate was used in this step solution was stirred at 75 °C for 12 h. The reaction product 33 was characterized by mass spectra and NMR. silica gel chromatography using 95% hexane and 5 % (0.156 mole) of lithium sulfide was added and the was cooled to room temperature and then 51.7 g of nesylate IV was added in 90 ml DMSO. The reaction nto a 1900 ml of 5% acetic aqueous solution with Continued the reaction until the reaction was there was no need for further purification. completed.

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# Step 3. Oxidation of the mitre product 33 to the sulfone 2-((2-benryl-4-mitrephenylsulfenyl)mothyl)-2-ethylhomanal (36)

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The procedure used to oxidize the sulfide 33 to the sulfone 34 has been previously described.

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Step 4. Reduction of 34 to 2-((2-benryl-4-hydroxymminophenylsulfonyl)methyl)-2-ethylhoxonal (35)

A 15 g sample of 34 was dissolved in 230 ml of ethanol and placed in a 500 ml rb flask under nitrogen. Next 1.5 g of 10 wt.% Pd/C was added and hydrogen gas was bubbled through the solution at room temperature until the nitro substrate 34 was consumed. The reaction could be readily monitored by silica gel TLC using 80/20 hexane/EtOAc. Product 35 was isolated by filtering off the Pd/C and then stripping off the EtOH solvent. The product was characterized by NMR and mass spectra.

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butoxy-carbonyl)hydroxynaminophonylculfonyl)acthyl)-2ethylhoxanal (36).

A 13.35 g sample of 35 (0.0344 mole) in 40 ml of dry (3cth)

THF was stirred in a 250 ml round bottomed flask. Next added 7.52 g (0.0344 mole) of dl-t-butyl dicarbonate in 7 ml THF. Heated at 60 °C overnight. Striped off THF and redissolved in methylene chloride. Extracted with 1 % HCl; and then 5% sodium bicarbonate.

The product was further purified by column chromatography using 90/10 hexane/ethyl acetate and then 70/30 hexane/ethyl acetate. The product 36 was obtained (4.12 g) which appeared to be mainly the di-(t-butoxycarbonyl) derivatives by proton NMR.

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A 250ml 3-neck round bottomed flask was charged with 4 g of 36 (6.8 mmoles), and 100 ml of anhydrous THF and cooled to -78 °C under a nitrogen atmosphere. Slowly add 2.29 g potassium tert-butoxide(20.4 mmoles) with

g) and BOC- 38 (0.78 g). using 85% hexane and 15 % ethyl acetate; BOC-37 (0.71 The isomers were separated by silica gel chromatography NMR were the two BOC protected isomers of 37 and 38. dried over sodium sulfate. The only products by TLC and ether phases were washed with saturated NaCl and then organic was removed from the water phase. The combined Striped off most of the THF and added to separatory funnel and extracted with ether until all of the the reaction mixture at -10 °C and stirred for 5 min. and the temperature was brought to -10 °C by means of a After 1 h at -78 °C the addition of base was completed remained by TLC. Next add 35 ml of deionized water to ice/salt bath. After 3 h at -10 °C, only trace 36 stirring and maintaining a -78 °C reaction temperature

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was isolated. Isomer 37 could be obtained in a similar sodium sulfate. After removing the ether, 0.665 g of 38 ether and water and then dried the ether layer with transferring to a separatory funnel extracted with and 16.5 ml ether and stirred until clear. After of sodium acetate (34.8 mmoles) to the reaction mixture 0.87 g of BOC-38 (1.78 mmoles) with 8.7 ml of 4 M HCl Next the BOC protecting group was removed by reacting (34.8 mmoles)in dioxane for 30 min. Next added 4.74 g

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xample 23

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(PE)

hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepina-1,1-5-phony1-2,3,6,5-totrahydrobonzothiepine-1,1-dioxide dioxide (41) (40) and (30,4b,5b) 3-Butyl-3-ethyl-7-(n-hoxylamino)-4-(3a, da, 5a) 3-Butyl-3-ethyl-7-(n-hewylamino)-d-hydroxy-

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Step 1. 2-((2-Bonzyl-4-(n-

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hexylamino)phonylsulfonyl)methyl)-2-ethylhexannl (39)

mmoles) and dissolved in 3.8 ml of ethanol under In a Fischer porter bottle weighed out 0.5 g of 30 (1.2

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nitrogen. Next added 0.1 g of Pd/C and 3.8 ml of hexane ethyl acetate and gradually increasing the isolated by column chromatography (0.16 g) using 90/10 removing the solvent by rotary evaporation 39 was Stirred for 48 h. After filtering off the catalyst and hexanal. Seal and pressure to 50 psi of hydrogen gas. was characterized by NMR and mass spectra. mobile phase to 70/30 hexane/ethyl acetate. The product

A 2-neck, 25 ml round bottomed flask with stir bar was Stop 2. (3a, 4a, 5a) 3-Butyl-3-ethyl-7-(n-hoxylamino)-4tetrahydrobenzothiepine-1,1-dioxide (41) 46 hydroxy-5-phonyl-2,3,6,5-tetrahydrobenzothiepine-1,1dioxide (40) and (3a,4b,5b) 3-Butyl-3-ethyl-7-(nhoxylamino)-4-hydroxy-5-phenyl-2,3,4,5-(40)

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ml of chilled 10% HCl and stirred at -10 °C for 5 min. of the starting material was consumed by TLC and only tert butoxide (0.335 mmole). After 15 min at -10 °C all charged with 0.158 g 39 (0.335 mmole) and 5 ml ether. Dried over sodium sulfate. Proton NMR of the of a salt/water bath. Slowly add 0.113 g of potassium anhydrous THF under nitrogen. Cool to -10 °C by means mobile phase to 70/30 hexane/ethyl acetate. 40 ( 53.2 the two isomers 40 and 41. The two isomers were dried product (0.143 g) indicated only the presence of the two isomers 40 and 41 were observed. Next added 5 mg); &1(58.9 mg). hexane ethyl acetate and gradually increasing the separated by silica gel chromatography using 90/10 Transferred to a separatory funnel and extract with

"Et (41)

Quaternization of amine substrates 40 and 41

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alkylated to quaternary salts by reaction with alkyl halides. For example 40 in DMF with 5 equivalents of Amine products such as 40 and 41 can be readily

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methyl iodide in the presence of 2,6 dimethyl lutidine produces the dimethylhexylamino quaternary salt. (5) The (42)

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-(4-iodophenyl)-2, 3, 4, 5-tetrahydrobenzothiepine-1, 1-dioxide (42) In a 25 ml round bottomed flask 0.5 g (1.3 mmole) of 6d of dry methylene chloride with stirring. Next 0.34 g of spectrum indicated a mixture of 6d , mono iodide 42 and chromatography and 42 was characterized bt NMR and mass with 50 ml methylene chloride and washed with 10 ml of codine was added and the solution was stirred at room a diiodide adduct. The mixture was separated by column , 0.67 g of mercuric triflate were dissolved in 20 ml temperature for 30 h. The reaction was then diluted See Tetrahedron, Vol.50, l M sodium thiosulfate; 10 ml of saturated KI; and No. 17, pp 5139-5146 (1994) Bachki, F. Et al.Mass dried over sodium sulfate.

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Spectra.

(2) 50, 40, 51)

Example 26

(30, 40, 52)

(30, 40, 55)

3-Butyl-5-(4-carbomethoxyphenyl)-3-ethyl-4hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (43)

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overnight. The catalyst was filtered and a high yield methanol, 38 ul triethylamine (0.275 mmole), 0.3 ml toluene and 37 mg of palladium chloride (0.21 mmole) was charged to a glass lined mini reactor at 300 psi carbon monoxide. The reaction was heated at 100 °C A 0.1 g sample of 42 ( 0.212 mmole), 2.5 ml dry of product was isolated.

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The product was characterized by NMR and mass spectra.

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Note the ester functionalized product 43 can be converted to the free acid by hydrolysis.

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Example 27

nethoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-[48], and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-Hoxide (49)

Step 1. 2-Mercapto-5-methoxybenzophenone (50)

Reaction of 66.2 g of 4-methoxythiophenol with 360 ml of 2.5 N n-butyllithium, 105 g of

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in 600 ml cyclohexane according to the procedure in WO distilled to remove 4-methoxythiophenol and gave 43.86 tetramethylethylenediamine and 66.7 g of benzonitrile 93/16055 gave 73.2 g of brown oil which was kugelrohr g of crude 50 in the pot residue.

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Step 2. 2-((2-Benzoyl-4-methoxyphenylthio)methyl)-2-1,000,1 ethylbexanal (51)

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procedure for the preparation of 2 gave 10.5 g of crude product which was purified by HPLC (5% ethyl acetate-Reaction of 10 g (0.04 mole) of crude 50 with 4.8 g triethylamine in 50 ml of diglyme according to the (0.02 mole) of mesylate 1 and 3.2 ml (0.23 mole) of hexane) to give 1.7 g (22%) of 51 8tep 3. 2-((2-Benzoyl-4-methoxyphenylsulfonyl)methyl). 15. 75. 75. (52) 2-ethyl-hexanal (52)

of 50-60% MCPBA according to the procedure of step 2 of procedure A in example 18 gave 1.16 g (90%) of 52 as a methylene chloride was reacted with 2.0 g (6.2 mmoles) A solution of 1.2 g (3.1 mmoles) of 51 in 25 ml of yellow oil.

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8tep 4. 2-((2-Benzyl-4-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (53)

yellow oil (1.1 g). of step 3 of procedure A of example 18 gave 53 as a Hydrogenation of 1.1 g of 52 according to the procedure

dioxide (49) methoxy-5-phony1-2,3,4,5-tetrahydrobenzothiepine-1,1-(48), and (3a, 4b, 5b) 3-Butyl-3-ethyl-4-hydroxy-7-5-phony1-2,3,4,5-totrahydrobenzothlepino-1,1-dioxide Stop 5. (3a, 6a, 5a) 3-Butyl-3-ethyl-4-bydroxy-7-methoxy. \* (S) Fet (49)

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mp 153-154 °C and 90 mg (8%) of 49 as solid, mp 136-140 purified by HPLC to give 40 mg (4%) of 48 as crystals, example 18 to give 1.07 g of a crude product which was for 2 h and worked up as in step 4 of procedure A of butoxide and 25 ml of anhydrous THF was held at reflux A solution of 1.1 g of 53, 0.36 g of potassium t-

5-Phanyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohowane

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Example 28

Step 1. 1-(Hydroxymethyl)-cyclohexanocarboxaldehyda (54)

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NMR and mass spectra were consistent with the product brine, and dried over sodium sulfate and concentrated chloride. The organic layer was washed with water, under vacuum to give 75 g (59.7%) of thick oil. Proton was diluted with water and extracted with methylene was evaporated to remove methanol. The reaction mixture mixture was stirred at room temperature over 48 then 90 ml of 1 N Sodium hydroxide in 1 h. formaldehyde in 225 ml of methanol was added dropwise cyclohexanecarboxaldehyde, 76.5 g of 37% of To a cold (O'C' mixture of 100 g (0.891 mole) of The reaction

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Stop 2. 1-(mesyloxymethyl)cyclohexanecarboxaldehyde

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acidified with conc. HCl and extracted with methylene temperature for 18 h then quenched with water, chloride. The reaction mixture was stirred at room pyridine (47.96 g, 0.57 mole) in 40 ml of methylene 80 ml of methylene chloride was added a solution of and 65.29 g (0.57 mole) of methanesulfonyl chloride in To a cold (0°C'mixture of alcohol 56 (75 g; 0.54 mole) under vacuum to give 91.63 g (77.8%) of thick oil. brine, and dried over sodium sulfate and concentrated chloride. The organic layer was washed with water, Proton NMR and mass spectra were consistent with the

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Stop 3. 1-((2-

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Benroylphenylthio)methyl)cyclohexanocarbonaldehyde (56)

and concentrated under vacuum to remove excess diglyme cooled, poured into dil. HCl and extracted with stirred and held at reflux for 24 h. The mixture was 32 g of triethylamine, and 150 ml of diglyme was A mixture of 69 g (0.303 mole) of 2-NMR and mass spectra were consistent with the product Hexane) and gave 18.6 g (75.9%) of yellow oil. Proton This was purified by silica gel flush column (5% EtOAc 10% NaOH, water, brine, and dried over sodium sulfate methylene chloride. The organic layer was washed with mercaptobenzophenone, 82 g (0.303 mole) of mesylate 55

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Step 6. 5-Phonyl-2,3-dihydrospirobonzothiepina-3,1'cyclohexane (57)

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mixture was held at reflux for 18 h. The mixture was mixture was heated to reflux for 2 h. A solution of DME was added TiCl, (16.8 g, 0.108 mole) . The reaction To a mixture of 6.19 g of zinc dust and 100 ml of dry added dropwise to the reaction mixture in 1 h and the compound 56 (8.3 g, 0.023 mole) in 50 ml of DME was

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cooled, poured into water and extracted with ether. The concentrated under vacuum. The residue was purified by organic layer was washed with water, brine, and dried HPLC (10% EtOAc: Hexane) to give 4.6 g (64%) of white solid, mp 90-91 °C. Proton and carbon NMR and mass over sodium sulfate, filtered through celite and spectra were consistent with the product.

Example 29

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8b-Phenyl-1a,2,3,8b-totrahydrospiro(bannothiopino[6,5b]oxirono-2,1'-cyclohomane)-4,d-dioxido (58)

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52.6 mmole) portionwise with spatula. The reaction was concentrated under vacuum to give 5 g of crude product. This was recrystallized from Hexane/EtOAc to give 4.31 chloroform under nitrogen was added 55% MCPBA (16.5 g, held at reflux for 18 h and washed with 10% NaOH(3X), carbon NMR and mass spectra were consistent with the g (81%) of yellow solid, mp 154-155 °C. Proton and water, brine, and dried over sodium sulfate and To a solution of 57 (4.6 g, 15 mmole) in 50 ml product.

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Example 30

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piro(benrothispine-3,1'-cyclohaxans)-1,1-dianide (59) trans-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro (54)

Pd/C catalyst was hydrogenated with 70 psi hydrogen for 3 h at room temperature. The crude reaction slurry was filtered through Celite and evaporated to drymess. The EtOAc-Hexane). The first fraction was 300 mg (60%) as a white solid, mp 99-100 °C. Proton NMR showed this was ethanol,10 ml of methylene chloride and 0.4 g of 10% residue was purified by HPLC (10% EtOAc-Hexane, 25% a trans isomer. The second fraction gave 200 mg of mixture of 0.5 g (1.4 mmoles) of 58 , 20 ml of solid which was impure cis isomer.

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cis-4-Hydroxy-5-phonyl-2,3,4,5-totrahydro

Example 31

upiro(benzothiepine-3,1'-cyclobexane)-1,1-dicaide (60) To a solution of 0.2 g (0.56 mmole) of 59 in 20 ml of CH,Cl,, was added 8 g of 50% NaOH and one drop of

(29) W. C. (62) 10 h at room temperature. Twenty g of ice was added to transfer catalyst. The reaction mixture was stirred for (3x10 ml) washed with water, brine and dried over MgSO, Aliquat-336 (methyltricaprylylammonium chloride) phase product. This was recrystallized from Hexane/EtOAc to the mixture and the mixture was extracted with CH,Cl, and carbon NVR and mass spectra were consistent with and concentrated in vacuo to recover 0.15 g of crude give 125 mg of white crystal, mp 209-210 °C . Proton the product.

cotradydrobonzothispine (61), and (3a,6b,5b) 3-Butyl-3-(30, 6a, 5a) 3-Butyl-3-othyl-4-hydroxy-5-phonyl-2,3,6,5athy1-4-hydroxy-5-phony1-2, 3, 4, 5-"ou (61) tetrahydrobenzothiepine (62) Example 32

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give 47 mg of 61 in the second fraction and 38 mg of 62 in the third fraction. Proton NMR and mass spectra were stirred at room temperature for 18 h and quenched with methylene chloride. The methylene chloride extract was fried over magnesium sulfate and concentrated in vacuo. To a solution of 0.5 g (1.47 mmole) of compound 47 in The residue was purified by HPLC (2% EtOAc-hexane) to ml of anhydrous THF was added 0.17 g (1.47 mmole) of 95% potassium t-butoxide. The reaction mixture was 10 ml of 10% HCl. The organic was extracted into consistent with the assigned structures

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2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (63) and 2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide(64) (3a, 6b, 5b) 3-Butyl-3-ethyl-4-hydroxy-7-amino-5-phenyl-(3a, 6a, 5a) 3-Butyl-3ethyl-d-hydroxy-7-amino-5-phenyl-

This same procedure was used to produce 64 from 38. vacuo and the only observable product was amine 63. catalyst was filtered and the solvent was removed in nitrogen the clave was charged with 100 psi hydrogen was consumed. After the reaction was complete the and mass spec and allowed to proceed until all of 37 and heated to 55 C. The reaction was monitored by TLC ethanol and .02 g 10 % Pd/C. After purging with An autoclave was charged with 200 mg of 37 in 40 cc

similar to that in Example 18 method B. compound 66, mp 115.5-117.5 °C, by the procedure converted to compound 65, mp 138.5-141.5 °C, and methoxybenzyl)phenol in 35% yield. This material was Chem. Soc. 2431 (1958) gave 4-methoxy-2-(3'chloride according to the procedure described in J. tetrahydrobenzothiepine-1,1-dioxide (66). Alkylation of e-methoxyphenol with 3-methoxybenzyl 7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5dioxide (65), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy. methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-(3a, 4a, 5a) 3-Buty1-3-ethy1-4-hydroxy-7-methoxy-5-(3'-Example 34 (65) 10'11 (66)

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tetrahydrobenzothiepine-1,1-dioxid tetrahydrobenzothiepine-1,1-dioxide (67), and (trifluoromethy1)pheny1)-2,3,4,5-(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3:-(trifluoromethyl)phenyl)-2,3,4,5-(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-

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similar to that in Example 18 method B. 194material was converted to compound 67, mp 226.5-228 °C. procedure described in J. Chem. Soc. 2431 (1958) gave Alkylation of 4-methoxyphenol with 3-4-methoxy-2-(3'-(trifluoromethyl)benzyl)phenol. This and compound 68, mp 188-190°C, byu the procedure (trifluoromethyl)benzyl chloride according to the

dioxide (69), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(4'tetrahydrobenzothiepine-1,1-dioxide (70) hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-(3a, 4a, 5a) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-X" Et (69) 450 A: 67 (70)

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Chem. Soc, 2431 (1958) gave 4-methoxy-2-(4'-Alkylation of 4-methoxyphenol with 4-fluorobenzyl chloride according to the procedure described in J. dioxide (71), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(3'hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1that in Example 18 method B. compound 69 and compound 70 by the procedure similar to fluorobenzyl)phenol. This material was converted to tetrahydrobenzothiepine-1,1-dioxide (72) fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-(3a,4a,5a) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-(11)

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Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'chloride according to the procedure described in J. Alkylation of 4-methoxyphenol with 3-fluorobenzyl fluorobenzyl) phenol. This material was converted to that in Example 18 method B. compound 71 and compound 72 by the procedure similar to

(3a,4a,5a) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (73), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (74).

Alkylation of 4-methoxyphenol with 2-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(2'-fluorobenzyl)phenol. This material was converted to compound 73 and compound 74 by the procedure similar to that in Example 18 method B.

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Example 39
(3a,4a,5a) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-a)
dioxide (75), and (3a,4b,5b) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(14-bydroxy-5-(3'-a) 4,5-tetrahydrobenzothiepine-1,1-bydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (76).

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Alkylation of 4-bromophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-bromo-2-(3'-methoxybenzyl)phenol. This material was converted to compound 75, mp 97-101.5 °C, and compound 76, mp 102-106 °C, by the procedure similar to that in Example 18 method B.

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Example 40 (30, (17) (3, 0) (3, 0) (3, 0) (3, 40, 5a) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5tetrahydrobenzothiepine-1,1-dioxide (77), and (3a,4b,5b) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5tetrahydrobenzothiepine-1,1-dioxide (78).

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Alkylation of 4-fluorophenol with 4-fluorobenzyl chloride according to the procedure described in J.

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Chem. Soc, 2431 (1958) gave 4-fluoro-2-(4'-fluorobenzyl)phenol. This material was converted to compound 77, mp 228-230 °C, and compound 78, mp 134.5-139 °C, by the procedure similar to that in Example 18 method B.

Example 41

(3a, 4a, 5a) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (79), and (3a,4b,5b) 3-Butyl-3-ethyl-7-fluoro-40hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (80).

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Alkylation of 4-fluorophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(3'-methoxybenzyl)phenol. This material was converted to compound 79, as a solid and compound 80, mp 153-155 °C by the procedure similar to that in Example 18 method

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(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (81).

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A mixture of 0.68 (1.66 mmol) of compound 77, 0.2 g (5 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at room temperature for 16 days. The reaction mixture was dilute with ether and washed with water and brine and dried over M<sub>5</sub>SO. The ether solution was concentrated in vacuo. The residue was purified by HPLC (20% ethyl acetate in hexanes). The first fraction was impure (3a,4a,5a) 3-butyl-3-ethyl-4-hydroxy-7-methylthio-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide. The second fraction was compound 81, mp 185-186.5 °C.

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(88)

tetrahydrobenzothiepine-1,1-dioxide (82). hydroxy-7-(1-pyrrolidinyl)-2,3,4,5-(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-

crystallized from ether-hexanes to give compound 82, mp A mixture of 0.53 g (1.30 mmol) of compound 78 and 5 ml reaction mixture was diluted with ether and washed with of pyrrolidine was held at reflux for 1 h. The 174.5-177 °C. solution was concentrated in vacuo. The residue was water and brine and dried over M<sub>s</sub>SO,. The ether

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tetrahydrobenzothiepine-1,1-dioxide (83). hydroxy-7-(1-morpholiny1)-2,3,4,5-(3a, 4b, 5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-

hexanes to give compound 83, mp 176.5-187.5 °C. vacuo. The residue was recrystallized from etherover M<sub>s</sub>SO<sub>1</sub>. The ether solution was concentrated in concentrated in vacuo. The residue was diluted with A mixture of 0.4 g (0.98 mmol) of compound 78 and 5.0 g ether (30 ml) and washed with water and brine and dried (56 mmol) of morpholine was held at reflux for 2 h and (83)

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tetrahydrobenzothiepine-1,1-dioxide (85). fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5dioxide (84), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(4'hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-(3a,4a,5a) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-

Chem. Soc. 2431 (1958) gave 4-methyl-2-(4'chloride according to the procedure described in J. fluorobenzyl)phenol). This material was converted to Alkylation of 4-methylphenol with 4-fluorobenzyl

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that in Example 18 method B compound 84 and compound 85 by the

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-(4. Example 46 8

tetrahydrobenzothiepine-1,1-dioxide (86), and hydroxyphenyl)-7-methoxy-2,3,4,5hydroxypheny1)-2,3,4,5-tetrahydrobenzothiepine-1,1-(3a,4b,5b) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-

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dioxide (87).

ml of methylene chloride was added 1.7 g (6.78 mmol) of To a solution of 0.52 (1.2 mmol) of compound 66 in 20 dried over M,SO,, and concentrated in vacuo. The and quenced with 2 N HCl. The organic was extracted and the reaction mixture was stirred at -78 °C for 1 h of boron tribromide was added to the reaction mixture 78 °C and was stirred for 4 min. An additional 0.3 ml born tribromide. acetate in hexanes). The first fraction was 0.11 g of into ether. The ether layer was washed with brine, give 0.04 g of compound 87 as a white solid, mp 264 °C compound 86 as a white solid, mp 171.5-173 °C. The residue (0.48 g) was purified by HPLC (30% ethyl second fraction was crystallized from chloroform to The reaction mixture was cooled to -

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Example 47 5 P (88)

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dioxíde (88). fluoropheny1)-2,3,4,5-tetrahydrobenzothiepine-1,1-(3a, 4b, 5b) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-

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compound 88 after an HPLC purification. room temperature and worked up as in Example 46 gave Reaction of compound 70 with excess boron tribromide at

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(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4tetrahydrobenzothiepine-1,1-dioxide (89) hydroxy-7-(1-azetidinyl)-2,3,4,5A mixture of 0.20 g (0.49 mmol) of compound 78, and 2.0 ather (30 ml) and washed with water and brine and dried g (35 mmol) of aztidine was held at reflux for 3 h and over MgSO4. The ether solution was concentrated on a concentrated in vacuo. The residue was diluted with steam bath. The separated crystals were filtered to steam bath. The separations, mp 196.5-199.5 °C. give 0.136 g of 89 as prisms, mp 196.5-199.5 °C.

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(F) hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dloxide (90). (3a,4b,5b) 3-Butyl-3-ethyl-5-(3'-(3a,4a,5a) 3-Butyl-3-ÉÉHyl-5-(3'-methoxyphenyl)-4methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5cetrahydrobenzothiepine-1,1-dioxide (91). (10) His example 49

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additional 1.4 mmol of sodium methanethiolate was added triturated with 100 ml of water and extracted methylene to the reaction mixture and the mixture was stirred at 60 °C for an additional 2 h. The reaction mixture was The first fraction (0.1 g) was compound 90, mp 117-121 A mixture of 0.4 g (0.95 nmol) of compound 79, 0.08 g °C. The second fraction (0.16 g) was compound 91, mp layer was dried over M,SO, and concentrated in vacuo. chloride. The methylene chloride water mixture was (1.14 mmol) of sodium methanethiolate and 15 ml of filtered through Celite and the methylene chloride anhydrous DMF was stirred at 60 °C for 2 h. An

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reaction mixture was stirred at room temperature for 16 h and then was held at reflux for 2 h and cooled before glycol dimethyl ether (DME) was held at reflux for 2 h. dried over MgSO, and concentrated in vacuo. The residue was purified by HPLC (hexane) to give 1.7 g (43%) of 3 purified by HPLC (hexane) to give 0.07 g (2%) of 4m in the earlier fraction and 0.1 g (3%) of 4b in the later methylene chloride. The methylene chloride extract was reaction mixture was added dropwise a solution of 3.54 being poured into brine. The organic was extract into (0.047 mole) of Ticl, and 80 mL of anhydrous ethylene as an oil in the first fraction. The second fraction A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g g (0.01 mole) of 2 in 30 mL of DME in 40 min. The was discarded and the third fraction was further The reaction mixture was cooled to 5 °C. To the fraction.

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### Example 2

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(5H)4-one-1,1-dioxide (5a) and trans-3-Butyl-3-ethyl-5phenyl-2, 3-dihydro-benzothiepin-(5H)4-one-1,1-dioxide cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(Sb

chloride. The reaction mixture was stirred for 20 h. An additional 1.2 g (1.75 mmole) of 50-60% MAPBA was added layer of the filtrate was washed with brine, dried over mmole) of a mixture of 4a and 4b in 10 mL of methylene and the reaction mixture was stirred for an additional (30%) of 5a as an oil in the first fraction and 0.17 g To a solution of 1.2 g (3.5 mmole) of 50-60% MCPBA in was purified by HPLC (5% EtOAc-hexane) to give 0.2 g insoluble solid was filtered. The methylene chloride MgSO,, and concentrated in vacuo. The residual syrup 3 h then was triturated with 50 mL of 10% NaOH. The 20 mL of methylene chloride was added 0.59 g (1.75 (26%) of 5b as an oil in the second fraction.

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A. Reduction of 5a and 5b with godium Borohydrido tetrahydrobenzothicpinc-1,1-dioxide (6d) (3a, 4b, 5b) 3-Butyl-3-othyl-4-hydroxy-5-phenyl-2,3,4,5tetrahydrobenzothiepino-1,1-dioxide (6c), and ethyl-6-hydroxy-5-phenyl-2,3,6,5benzothiepino-1,1-dioxido (6b), (3a,4a,5a) 3-Buty1-3-Butyl-3-othyl-4-hydroxy-5-phenyl-2,3,4,5-totrahydrotetrahydrobenzothiepino-1,1-dioxide (6a), (3a, 6b, 5a) 3-(3a, 6a, 5b) 3-Butyl-3-ethyl-4-hydroxy-5-phonyl-2,3,4,5-

Recrystallization from hexane gave a solid, mp 160-161 of 6d in the fourth fraction as a solid. was eluted with 30% EtOAc-hexane to give 0.08 g (12%) hexane gave a solid, mp 179-181 °C. Finally, the column the third fraction as a solid. Recrystallization from with 20% EtOAc-hexane to give 0.077 g (11%) of 6c in g (27%) of 6m as a syrup. The second fraction was 0.2 g 10% EtOAc-hexane as eluant. The first fraction was 0.18 two materials were combined and purified by HPLC using sodium borohydride in 10 mL of ethanol and was worked experiment, 0.45 g of 5a was treated with 0.44 g of and extracted with methylene chloride. The methylene (30%) of **6b** also as a syrup. The column was then eluted up as described above to give 0.5 g of syrup which was in vacuo to give 0.2 g of syrup. In a separate chloride extract was dried over MgSO, and concentrated remove ethanol. The residue was triturated with water temperature for 18 h and concentrated in vacuo to borohydride. The reaction mixture was stirred at room ethanol was added 0.24 g (6.4 mmole) of sodium To a solution of 0.22 g (0.59 mmole) of 5b in 10 mL of identical to the 0.2 g of syrup obtained above. These

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# B. Conversion of 6a to 6c and 6d with NaOH and PTC

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was stirred for 0.5 h at room temperature and was added CH,Cl, , was added 9 g of 40% NaOH. The reaction mixture and eluted with EtOAc-hexane to give 12.8 mg (4%) of 2components of this mixture were separated using an HPLC in vacuo to recover 0.17 g of a colorless film. The with CH<sub>2</sub>Cl<sub>3</sub> (3x10 ml), dried over MgSO, and concentrated treated with 25 mL of ice-crystals then was extracted one drop of Aliquat-336 (methyltricaprylylammonium fraction and 90.0 mg (31%) of 6d in the third fraction. first fraction, 30.9 mg (11%) of 6c in the second was stirred for 0.5 h at room temperature before being chloride) phase transfer catalyst (PTC). The mixture To a solution of 0.29 g (0.78 mmole) of 6a in 10 mL (2-benzylphenylsulfonylmethyl)-2-ethylhexenal in the

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## Oxidation of 6a to 5b

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mixture was poured into a ceramic filterfrit containing CH,Cl, was added 0.23 g (1.0 mmole) of pyridinium To a solution of 0.20 g (0.52 mmole) of 6a in 5 mL of a colorless oil. silica gel and was eluted with CH,Cl,. The filtrate was chlorochromate and stirred overnight. The dark reaction h then was treated with additional 0.23 g of pyridinium chlorochromate. The reaction mixture was stirred for 2 concentrated in vacuo to recover 167 mg (87%) of 5b as

Example 4

3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine-1,1dioxide (7)

triturated with 25 mL of water followed by 50 mL of 10% mixture was allowed to stir overnight under N, and was To a solution of 5.13 g (15.9 numole) of 3 in 50 mL of chloroperoxybenzoic acid) portionwise causing a mild (4x20 mL). The CH,Cl, extract was dried over MgSO, and CH,C1, was added 10 g (31.9 mmole) of 50-60% MCPBA (mreflux and formation of a white solid. The reaction NAOH solution. The organic was extracted into CH,Cl, evaporated to dryness to recover 4.9 g (87%) of an opaque viscous oil.

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#### Example 5

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tetrahydro-benzothiepino[4,5-b]oxirene-4,4-dioxide (8a) tetrahydro-benzothispino [4,5-b]oxirens-4,4-dioxids (lea, 2b, 8ba ) 2-Butyl-2-ethyl-8b-phenyl-la, 2, 3, 8b-(laa, 2a, 8ba) 2-Butyl-2-ethyl-8b-phenyl-1a, 2, 3, 8b-

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portionwise 5 g (14.1 mmole) of 50-60 % MCPBA causing a with brine, dried over MgSO,, and concentrated in vacuo extracted with 10% potassium carbonate (3x50 mL), once crystalline product in hexane recovered 141.7 mg (10%) mild exotherm. The reaction mixture was stirred under insoluble white slurry was filtered. The filtrate was HPLC gave 0.65 g of crystalline product. This product To 1.3 g (4.03 mole) of 3 in 25 mL of CHCl, was added to give 1.37 g of a light yellow oil. Purification by N, overnight and was then held at reflux for 3 h. The concentrated in vacuo to give 206 mg of white film which is a mixture of 30% 8a and 70% 8b by 'H NMR. is a mixture of two isomers. Trituration of this of a white crystalline product. This isomer was characterized by NMR and mass spectra to be the (laa,2b,8ba) isomer 8a. The hexane filtrate was

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Example 6

benrothispine-1,1-dioxide (9a), trans-3-Butyl-3-ethyl-(9b), and 3-Butyl-3-ethyl-4-bydroxy-5-cyclobexylidins-5-phenyl-1,3,4,5-tetrahydrobenzothiepine-1,1-dloxide cis-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydro-2,3,4,5-tetrahydrobenrothiepine-1,1-dioxide (10)

second fraction, 5.0 mg (4%), was a 50/50 mixture of 9a product believed to be 3-butyl-3-ethyl-4,5-dihydroxy-5dryness in vacuo to recover 0.117 g of a colorless oil. and 9b. The third fraction was 8.8 mg (6%) of 6a . The A mixture of 0.15 g (0.4 mmole) of a 3:7 mixture of 8a Fisher/Porter vessel, then was added 0.1 g of 10% Pd/C This material was purified by HPLC eluting with BtOAchexane. The first fraction was 4.2 mg (3%) of 9b. The based on mass spectrum. The sixth fraction was 7.5 mg for 5 h and filtered. The filtrate was evaporated to (5%) of a mixture of 6d and one of the isomers of 10, catalyst. This mixture was hydrogenated at 70 psi H, phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide fourth fraction was 25.5 mg (18%) of 6b. The fifth fraction was 9.6 mg (7%) of a mixture of 6b and a and 8b was dissolved in 15 ml MeOH in a 3 oz.

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#### Example 7

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under air was hydrogenated in 100 mL of methanol using product was purified by HPLC to give 0.9 g (25%) of 9b, 5b, 0.02 g (1%) of 6c, 0.06 g (2%) of one isomer of 10, 0.45 g (13%) of 9a, 0.27 g (7%) of 6a, 0.51 g (14%) of epoxidation of 3 with excess MCPBA in refluxing CHCl, 1 g of 10% Pd/C catalyst and 70 psi hydrogen. The 10a and 0.03 g (1%) of another isomer of 10, 10b. In another experiment, a product (3.7 g) from

#### Example 8

# 2-((2-Benzoylphenylthio)methyl)butyraldohydo (11)

HPLC (10% EtOAc-hexane) to give 5.6 g of pure 11. times to give 6.0 g of a syrup which was purified by washed with 50 mL of 1 M potassium carbonate threa This material was dissolved in ether (100 mL) and was indicating a reversed reaction during distillation. a fraction (12.2 g) which contained starting material by kugelrohr distillation at 0.5 torr (160-190 °C) gave hexane) to give 22 g (64%) of 11 in the second with dilute HCl, brine, and 1 M potassium carbonate. days , diluted with ether, and was washed successively fraction. An attempt to further purifiy this material in vacuo. The residue was purified by HPLC (10% EtOAc-The ether layer was dried over MgSO, and concentrated reaction mixture was stirred at room temperature for 3 followed by 13 g (0.128 mole) of triethylamine. The of 2-ethylacrolein in 40 mL of dry THF was added 24.6 g (0.116 mole) of 2-mercaptobenzophenone in 40 mL of THF To an ice bath cooled solution of 9.76 g (0.116 mole)

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#### Example 9

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## 3-Ethyl-5-phonyl-2,3-dihydrobonzothiepine (12)

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purified by HPLC to give 2.06 g (77%) of 12 as an oil MgSO, and concentrated. The residual oil (2.5 g) was filtered through Celite. The filtrate was dried over of 2.98 g (0.01 mole) of 11 was added dropwise in 1 h. in the second fraction. into ether. The ether layer was washed with brine and cooled and poured into water. The organic was extracted The reaction mixture was held at reflux for 18 h, reaction mixture was held at reflux for 2 h. A solution mL of DME was added 7.5 g (0.048 mole) of TiCl, The To a mixture of 2.61 g (0.04 mole) of zinc dust and 60

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### Example 10

benzothiepino-[4,5-b]oxireno-4,4-dioxide (13) (1aa, 2a, 8ba) 2-Ethyl-8b-phenyl-1a, 2, 3, 8b-tetrahydro-

portionwise causing an exothem and formation of a white CHCl, was added 6.8 g (19.4 mmole) of 50-60% MCPB slurried in 200 ml of warm Et,O and filtered to give overnight diluted with 100 ml methylene chloride and To a solution of 1.5 g (5.64 mmole) of 12 in 25 ml of 0.82 g (46%) of 13 as a white solid, mp 185-186.5 °C that only one isomer is present. This solid was recover 1.47 g of an off white solid. 'H NMR indicated then dried over MgSO, and evaporated to dryness to washed successively with 10% K,CO, (4x50 ml), water (twice with 25 ml) and brine. The organic layer was solid. The mixture was stirred at room temperature

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### Example\_11

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totrahydro-benzothicpine-1,1-dioxide (14a), (3a,4b,5b) sthyl-5-phenyl-2,3,4,5-totrahydro-benzothlepino-1,1tetrahydrobensothicpine-1,1-dioxide (14b), and cin-3-3-Ethyl-4-hydroxy-5-phonyl-2,3,6,5-(3a, 4b, 5a) - 3-Ethyl-4-hydroxy-5-phenyl-2, 3, 4, 5dioxide (15)

of a saturated NaHCO, solution followed by 89 g of with 70 psi hydrogen for 4 h. The crude reaction slurry acid and 0.5 g of 10% Pd/C catalyst was hydrogenated A mixture of 0.5 g (1.6 mole) of 13, 50 ml of acetic was filtered and the filtrate was stirred with 150 ml over MgSO, and concentrated in vacuo to give 0.44 g chloride (4x25 ml), then the organic layer was dried acetic acid. The mixture was extracted with methylene NaHCO, powder portionwise to neutralize the rest of first fraction, 272 mg (54%) of 16a as a solid, mp 142-HPLC (EtOAc-Hexane) to give 26.8 mg (6%) of 15 in the (87%) of a voluminous white solid which was purified by 143.5 °C, in the second fraction, and 35 mg (7%) of impure 16b in the third fraction.

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### Example 12

2-Ethyl-2-((2-Bydroxymethylphenyl)thicmethyl)hexenal (19

alcohol, 6.4 g (0.032 mole) of 1, 3.6 g (0.036 mole) of at reflux for additional 16 h. The reaction mixture was idded to the reaction mixture and the mixture was held mercaptobenzyl alcohol and 0.72 g of triethylamine was methylene chloride. The methylene chloride extract was A mixture of 5.0 g (0.036 mole) of 2-mercaptobenzyl triethylamine and 25 mL of 2-methoxyethyl ether was Purification by HPLC (20% EtOAc-hexane) gave 3.7 g cooled and poured into 6N HCl and extracted with washed twice with 10% NaOH, dried over MgSO, and concentrated in vacuo to give 9.6 g of residue. held at reflux for 7 h. Additional 1.1 g of (41%) of 16 as an oil.

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### Example 13

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# 2-Ethyl-2-((2-formylphenyl)thicmethyl)hexenal (17)

chloride eluant was purified by HPLC (20% ETOAc-hexane) through a bed of silica gel. The silica gel was eluted pyridinium chlorochromate, 2 g of Celite and 30 mL of methylene chloride was stirred for 18 h and filtered A mixture of 3.7 g of 16, 5.6 g (0.026 mole) of with methylene chloride. The combined methylene to give 2.4 g (66%) of an oil.

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### Example 14

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## 3-Butyl-3-ethyl-2,3-dihydrobenzothiepine (18)

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DME in 10 min. The reaction mixture was stirred at room reflux for 2 h and cooled to room temperature. To this mixture was added 2.4 g (8.6 mmole) of 17 in 20 mL of (0.047 mole) of TiCl,, and 50 mL of DME was held at A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g

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temperature for 2 h and held at reflux for 1 h then was chloride-water mixture was filtered through Celite. The a residue. Purification by HPLC gave 0.41 g (20%) of 18 over MgSO,, and concentrated in vacuo to give 3.0 g of methylene chloride layer was washed with brine, dried reaction mixture was poured into dilute HCl and was let standing at room temperature over weekend. The stirred with methylene chloride. The methylene as an oil in the early fraction.

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(laa,2a,8ba ) 2-Butyl-2-ethyl-la,2,3,8b-tetrahydrotetrahydro-benzothiepino[4,5-b]oxirene-4,4-dioxide benzothiepino[4,5-b]oxirene-4,4-dioxide (19a) and (laa, 2b, 8ba) 2-Butyl-2-ethyl-8b-phenyl-la, 2, 3, 8b-(19b)

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concentrated in vacuo. The residue was purified by HPLC and concentrated in vacuo. The residue was dissolved in Recrystallization from hexane gave 0.08 g (17%) of 194. To a solution of 0.4 g of 0.4 g (1.6 numole) of 18 in 30 mL of methylene chloride was added 2.2 g (3.2 mmole) of 30 mL of CHCl, and was held at reflux for 18 h under N,. 50-60% MCPBA. The reaction mixture was stirred for 2 h NaOH and 5 g of sodium sulfite. The methylene chloride (20% EttOAc-hexane) to give a third fraction which was further purified by HPLC (10% EtOAc-hexane) to give The reaction mixture was stirred with 100 mL of 10% layer was washed with brine, dried over MgSO, and 0.12 g of syrup in the first fraction.

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first fraction and 60 mg of 19b in the second fraction. fraction was combined with the second fraction and was further purified by HPLC to give additional 19a in the mp 89.5-105.5 °C. The mother liquor from the first Crystallization from hexane gave 56 mg of a white

### Example 16

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3-Butyl-3-othyl-4,5-dihydroxy-5-phonyl-2,3,4,5-tetrnhydro-bonzothiopine-1,1-dioxide (20)

This product was isolated along with 6b from hydrogenation of a mixture of 8a and 8b.

#### xample 17

3-Buty1-3-othy1-4-hydroxy-5-pheny1thio-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (21)

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21c, respectively, by 'H NMR and mass spectra. were three different isomers of 21, i.e. 21s, 21b, and second fraction and 11 mg of a third fraction which hexane to give 17 mg of a first fraction, 4 mg of a disulfide. This material was purified by HPLC (5% fraction. The column was then eluted with 20% EtOAc-EtOAc-hexane) to remove diphenyl disulfide in the first which contain substantial amounts of diphenyl and concentrated in vacuo to give 0.19 g of semisolid successively with 10% NaOH and brine, dried over MgSO, chloride. The methylene chloride layer was washed poured into water and extracted with methylene mmole) of thiophenol, 0.37 g (2.7 mmole) of potassium carbonate, and 4 mL of DMF was stirred at room A mixture of 25 mg (0.085 mmole) of 19b, 0.27 g (2.7 temperature under  $N_{_{\! 2}}$  for 19 h. The reaction mixture was

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#### Example 18

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Alternative Synthesis of 6c and 6d

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A. Proparation from 2-((2-Benroylphenylthio)methyl)-2-othylhexanal (2)

Step 1. 2-((2-Bonzoylphenylsulfonyl)methyl)-2-othylhoxanal (44)

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To a solution of 9.0 g (0.025 mole) of compound 2 in 100 ml of methylene chloride was added 14.6 g (0.025 mol) of 50-60% MCPBA portionwise. The reaction mixture was stirred at room temperature for 64 h then was stirred with 200 ml of 1 M potassium carbonate and

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filtered through Celite. The methylene chloride layer was washed twice with 300 ml of 1 M potassium carbonate, once with 10% sodium hydroxide and once with brine. The insoluble solid formed during washing was removed by filtration through Celite. The methylene chloride solution was dried and concentrated in vacuo to give 9.2 g (95%)of semisolid. A portion (2.6 g) of this solid was purified by HPLC(10% ethyl acetate-hexane) to give 1.9 g of crystals, mp 135-136 °C

# stop 2. 2-((2-Benzylphonylgulfonyl)mothyl)-2ethylhomanal (45)

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A solution of 50 g (0.13 mole) of crude 44 in 250 ml of methylene chloride was divided in two portions and charged to two Fisher-Porter bottles. To each bottle was charged 125 ml of methanol and 5 g of 10% Pd/C. The bottles were pressurized with 70 psi of hydrogen and the reaction mixture was stirred at room temperature for 7 h before being charged with an additional 5 g of 10% Pd/C. The reaction mixture was again hydrogenated with 70 psi of hydrogen for 7 h. This procedure was repeated one more time but only 1 g of Pd/C was charged to the reaction mixture. The combined reaction mixture was filtered and concentrated in vacuo to give 46.8 g of 45 as brown oil.

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gtep 3. (3a, da, 5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl2,3,6,5-tetrahydrobonzothiepine-1,1-dioxido (6c), and
(3a, db, 5b) 3-Butyl-3-ethyl-6-hydroxy-5-phenyl-2,3,6,5tetrahydrobenzothiepine-1,1-dioxide (6d)

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To a solution of 27.3 g (73.4 mmole) of 45 in 300 ml of anhydrous THF cooled to 2 °C with an ice bath was added 9.7 g (73.4 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred for 20 min, quenched with 300 ml of 10% HCl and extracted with methylene chloride. The methylene chloride layer was dried over magnesium sulfate and concentrated in vacuo to give

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24.7 g of yellow oil. Purification by HPLC (ethyl acetate-hexane) yielded 9.4 g of recovered 45 in the first fraction, 5.5 g (20%) of 6c in the second fraction and 6.5 g (24%) of 6d in the third fraction.

## B. Proparation from 2-hydroxydiphonylmethane Step 1. 2-mercaptodiphenylmethane (46)

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mixture was stirred at room temperature for 30 min then has extracted into 500 ml of toluene. The toluene layer reaction mixture was stirred at room temperature for 18 h before being poured into 300 ml of water. The organic brine and was concentrated in vacuo to give 78.6 g of a concentrate HCl, The oily suspension was extracted into yellow oil which was 95% pure dimethyl 0-2-benzylphenyl residue was kugelrohr distilled at 1 torr (180-280 °C). to give 37.3 g (46%) of the rearranged product dimethyl temperature was maintained below 30 °C by an ice-water the distillate (56.3 g) was crystallized from methanol mixture of 57 g (0.21 mole) of this yellow solid, 30 g residue was diluted with 200 ml of water and extracted sodium hydride oil dispersion. The sodium hydride was was washed successively with 10% sodium hydroxide and thiocarbamate. This oil was heated at 280-300 °C in a stirred overnight then was concentrated in vacuo. The hydroxydiphenylmethane in 200 ml of DMF in 1 h while To a 500 ml flask was charged 16 g (0.33 mol) of 60% flask was charged 100 ml of DMF. To this mixture was cooled with an ice bath. To the reaction mixture was  $S extsf{-}2 extsf{-}$ benzylphenyl thiocarbamate as a yellow solid. A washed twice with 50 ml of hexane. To the reaction chloride at once. The ice bath was removed and the with ether. The aqueous layer was made acidic with bath. After complete addition of the reagent, the added 49.4 g (0.4 mole) of dimethyl thiocarbamoyl sugelrohhr pot under house vacuum for 30 min. The of potassium hydroxide and 150 ml of methanol was ether. The ether extract was dried over magnesium added a solution of 55.2 g (0.3 mol) of 2-

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sulfate and concentrated in vacuo. The residue was crystallized from hexane to give 37.1 g (88%) of 2-mercaptodiphenylmethane as a yellow solid.

# Step 2. 2-((2-Bensylphonylthio)methyl)-2-othylhowannl (47)

A mixture of 60 g (03 mole) of yellow solid from step 1, 70 g (0.3 mole) of compound 1 from preparation 1, 32.4 g (0.32 mole) of triethylamine, 120 ml of 2-methoxyethyl ether was held at reflux for 6 hr and concentrated in vacuo. The residue was triturated with 500 ml of water and 30 ml of concentrate HCl. The organic was extracted into 400 ml of ether. The ether layer was washed successively with brine, 10% sodium hydroxide and brine and was dried over magnesium sulfate and concentrated in vacuo. The residue (98.3 g) was purified by HPLC with 2-5% ethyl acetate-hexane as eluent to give 2-((2-benzylphenylthio)methyl)-2-ethylhexanal 47 as a yellow syrup.

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## 8top 3. 2-((2-Benzylphenylsulfonyl)mothyl)-2ethylhezanal (45)

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To a solution of 72.8 g (0.21 mole) of yellow syrup from step 2 in 1 liter of methylene chloride cooled to 10 °C was added 132 g of 50-60% MCPBA in 40 min. The reaction mixture was stirred for 2 h. An additional 13 g of 50-60% MCPBA was added to the reaction mixture. The reaction mixture was stirred for 2 h and filtered through Celite. The methylene chloride solution was washed twice with 1 liter of 1 M potassium carbonate then with 1 liter of brine. The methylene chloride layer was dried over magnesium sulfate and concentrated to 76 g of 2-((2-benzylphenylsulfonyl)methyl)-2-ethylhexanal 45 as a syrup.

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Stop 4. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydrozy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (60), and

tetrahydrobenzothiepine-1, 1-dloxide (6d) (3a, 4b, 5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-

the procedure in step 3 of procedure A gave pure 6c and Reaction of 45 with potassium t-butoxide according to 6d after HPLC

### Example 19

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phony1-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (26) phenylthio)methyl)-2-ethylhexanal (22) Step 1. Preparation of 2-((2-benzoyl-4-methoxy and (3a,4a,5a) 3-Butyl-3-athyl-4-hydroxy-8-methoxy-5phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (25) (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-

described below procedure which avoided a chromatography step was  $260~^\circ\mathrm{C}$  as previously described. The improved isolation reacting the thiocarbamate (5 g) in diphenyl ether at needed. The thermal rearrangement was performed by improved isolation procedure no chromatography was previously described in example 18. The product can be dimethyl 0-2-benzoyphenyl thiocarbamate by methods isolated by recrystallization from ethanol. Using this 2-Hydroxy-4-methoxybenzophenone was converted to the

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by rotary evaporation the solution was extracted with 5 3.5 g of KOH for 4 h. After removing THF and methanol 2-mercapto-4-methoxybenzophenone (2.3 g) was isolated titrating the desired mercaptan into base with limited thiophenol product. The product was further purified by extracted with ether to obtain a 2.9 g of crude % NaOH and ether. The base layer was acidified and KOH. After acidification and extraction with ether pure 100 ml of methanol and 100 ml of THF in the presence of The crude pyrolysis product was then heated at 65 °C

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converted to the 2-((2-benzoy1-4-2-mercapto-4-methoxybenzophenone can readily be

previously described. reaction with 2-ethyl-2-(mesyloxymethyl)hexanal (1) as methoxyphenylthio)methyl)-2-ethylhexanal (22) by

2-ethylhexanal (23) Step 2. 2-((2-Benzoyl-5-methoxyphenylsulfonyl)methyl)-

Substrate 22 was readily oxidized to 2-((2-benroy1-5methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (23) as described in example 18.

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ethylhexanal (24) step 3. 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-

described in example 18. methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (24) as Sulfone 23 was then reduced to 2-((2-benzyl-5-

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methoxy-5-pheny1-2,3,4,5-tetrahydrobenzothiepine-1,1-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide Step 4. (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-(25) and (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-8dioxide (26)

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ၾ with 19.8 g (0.05 mole) of sulfone 24 in 100 ml dry A 3-neck flask equipped with a powder addition solution was maintained at -1.6 °C. After 30 min g (0.05 mole) of potassium t-butoxide by means of the THF. The reaction was cooled to -1.6 °C internal funnel, thermocouple and nitrogen bubbler was charged reaction 400 ml of cold ether was added and this powder addition funnel. The resulting light yellow temperature by means of ice/salt bath. Slowly add 5.61 dryness to obtain 19.9 g of product. 'H mmr and glpc magnesium sulfate and after filtration stripped to The organic layers were combined and dried over layer was extracted with 300 ml of methylene chloride. solution was extracted with cold 10 % HCl. The acid indicated a 96% conversion to a 50/50 mixture of 25 and

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 $26.\ {\rm The\ only\ other\ observable\ compound\ was\ 4\$\ starting\ sulfone\ 24.}$ 

The product was then dissolved in 250 ml of 90/10 hexane/ethyl acetate by warming to 50 °C. The solution was allowed to cool to room temperature and in this way pure 26 can be isolated. The crystallization can be enhanced by addition of a seed crystal of 26. After 2 crystallizations the mother liquor which was now 85.4% 25 and has a dry weight of 8.7 g. This material was dissolved in 100 ml of 90/10 hexane/ethyl acetate and 10 ml of pure ethyl acetate at 40 C. Pure 25 can be isolated by seeding this solution with a seed crystal of 25 after storing it overnight at 0 C.

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(38,40,5a) 3-Butyl-3-othyl-4,8-dihydroxy-5-phenyl-2,3,4,5-totrahydrobensothiepine-1,1-dioxide (27)

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In a 25 ml round bottomed flask, 1 g of 26(2.5 mmoles) and 10 ml methylene chloride were cooled to - 78 °C with stirring. Next 0.7 ml of boron tribromide(7.5 mmole) was added via syringe. The reaction was allowed to slowly warm to room temperature and stirred for 6 h. The reaction was then diluted with 50 ml methylene chloride and washed with saturated NaCl and then water. The organic layer was dried over magnesium sulfate. The product (0.88g) 27 was characterized by NMR and mass spectra.

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#### Example 21

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## General Alkylation of phenol 27

A 25 ml flask was charged with 0.15 g of 27(0.38 mmole), 5 ml anhydrous DMF, 54 mg of potassium carbonate(0.38 mmole) and 140 mg ethyl iodide (0.9 mmole). The reaction was stirred at room temperature overnight. The reaction was diluted with 50 ml ethyl ether and washed with water (25 ml) then 5% NaOH (20 ml) and then sat. NaCl. After stripping off the solvent

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the ethoxylated product 28 was obtained in high yield. The product was characterized by NWR and mass spectra. This same procedure was used to prepare products listed in table 1 from the corresponding iodides or bromides. For higher boiling alkyl iodides and bromides only one equivalent of the alkyl halide was used.

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#### Example 22

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(3a, da, 5a) 3-Butyl-3-othyl-4-hydroxy-7-hydroxyemino-5-phenyl-2,3,4,5-tetrahydrobenzothiepino-1,1-dioxido (37) and (3a, db, 5b) 3-Butyl-3-othyl-4-hydroxy-7-hydroxyemino-5-phenyl-2,3,4,5-tetrahydrobenzothiopino-1,1-dioxide (38)

Stop 1. Preparation of 2-chloro-5-nitrodiphenylmothane

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Procedure adapted from reference :Synthesis -Stuttgart 9 770-772 (1986) Olah G. Et al

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poured into a chilled stirred solution of 1600 ml of combined with two 500 ml methylene chloride extractions layers. The methylene chloride layer was isolated and Poured into a 4 liter separatory funnel and separated saturated sodium bicarbonate. Gas evolution occurred 12 h under nitrogen. The reaction mixture was then to slowly warm up to room temperature and stirred for the additions were completed the reaction was allowed sulfonic acid and triethylsilane)were repeated. After solution. Both addition steps (trifluoromethane acid in 345 ml methylene chloride was added slowly. methylene chloride was added dropwise to the chilled Next 30 g of triethylsilane (0.172 mole) in 345 ml methylene chloride and the solution was cooled to funnel, 150 g( 0.172 mole) of trifluoromethane sulfonic ice/water temperature. By means of an additional Under nitrogen, a 3 neck flask was charged with 45 g (0.172 mole ) of 2-chloro-5-nitrobenzophenone in 345 ml

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of the aqueous layer. The methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from hexane to give 39 g product. Structure 32 was confirmed by mass spectra and proton and carbon NMR.

## Stop 2. Proparation of 2-((2-bensyl-4nitrophenylthio)methyl)-2-ethylhexanal (33)

8 ₽ 5 ĸ was cooled to room temperature and then 51.7 g of flask with water condenser. Next 150 ml DMSO and 7.18 g 0.156 mole) from above was placed in a 2 liter 2 neck The 2-chloro-5-nitrodiphenylmethane product 32 (40 g. ethyl acetate. If pure mysylate was used in this step silica gel chromatography using 95% hexane and 5 % over MgSO4. After removal of ether, 82.7 g of product stirring, extracted with 4 x 700 ml of ether, and dried completed. Next the reaction mixture was slowly poured Continued the reaction until the reaction was monitored by TLC and added more mysylate if necessary. mixture was heated to 80 °C under nitrogen. After 12 h mesylate IV was added in 90 ml DMSO. The reaction solution was stirred at 75 °C for 12 h. The reaction there was no need for further purification. The was isolated. The material can be further purified by into a 1900 ml of 5% acetic aqueous solution with  $(0.156 \ \mathrm{mole})$  of lithium sulfide was added and the product 33 was characterized by mass spectra and NMR

gtop 3. Oxidation of the nitro product 33 to the sulfono 2-((2-bensyl-4-nitrophonylsulfonyl)mothyl)-2ethylhomenal (36)

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The procedure used to oxidize the sulfide 33 to the sulfone 34 has been previously described.

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Stop 4. Reduction of 34 to 2-((2-benzyl-4-hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (35)

A 15 g sample of 34 was dissolved in 230 ml of ethanol and placed in a 500 ml rb flask under nitrogen. Next 1.5 g of 10 wt. & Pd/C was added and hydrogen gas was bubbled through the solution at room temperature until the nitro substrate 34 was consumed. The reaction could be readily monitored by silica gel TLC using 80/20 hexane/EtOAc. Product 35 was isolated by filtering off the Pd/C and then stripping off the EtOH solvent. The product was characterized by NMR and mass spectra.

step 5. Proparation of the 2-((2-bensyl-6-N,0-di-(tbutoxy-carbonyl)hydroxyaminophenylsulfonyl)mothyl)-2othylboxenal (36).

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g) and BOC- 38 (0.78 g).

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A 13.35 g sample of 35 (0.0344 mole) in 40 ml of dry THF was stirred in a 250 ml round bottomed flask. Next added 7.52 g (0.0344 mole) of di-t-butyl dicarbonate in 7 ml THF. Heated at 60 °C overnight. Striped off THF and redissolved in methylene chloride. Extracted with 1 % HCl; and then 5% sodium bicarbonate.

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The product was further purified by column chromatography using 90/10 hexane/ethyl acetate and then 70/30 hexane/ethyl acetate. The product 36 was obtained (4.12 g) which appeared to be mainly the di-(t-butoxycarbonyl) derivatives by proton NMR.

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Step 6. (3a, da, 5a, 3-Butyl-3-othyl-4-hydroxy-7hydroxyamino-5-phonyl-2,3,4,5-totrahydrobonsothiopina-1,1-dioxide (37) and (3a, db, 5b) 3-Butyl-3-othyl-4hydroxy-7-hydroxyamino-5-phanyl-2,3,4,5totrahydrobonsothiopino-1,1-dioxide (38)

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A 250ml 3-neck round bottomed flask was charged with 4 g of 36 (6.8 mmoles), and 100 ml of anhydrous THF and cooled to -78 °C under a nitrogen atmosphere. Slowly add 2.29 g potassium tert-butoxide(20.4 mmoles) with stirring and maintaining a -78 °C reaction temperature. After 1 h at -78 °C the addition of base was completed and the temperature was brought to -10 °C by means of a

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ice/salt bath. After 3 h at -10 °C, only trace 36 remained by TLC. Next add 35 ml of deionized water to the reaction mixture at -10 °C and stirred for 5 min. Striped off most of the THF and added to separatory funnel and extracted with ether until all of the organic was removed from the water phase. The combined ether phases were washed with saturated NaCl and then dried over sodium sulfate. The only products by TLC and NMR were the two BOC protected isomers of 37 and 38. The isomers were separated by silica gel chromatography using 85% hexane and 15 % ethyl acetate; BOC-37 (0.71

Next the BOC protecting group was removed by reacting 0.87 g of BoC-38 (1.78 mmoles) with 8.7 ml of 4 M HCl (34.8 mmoles) in dioxane for 30 min. Next added 4.74 g of sodium acetate (34.8 mmoles) to the reaction mixture and 16.5 ml ether and stirred until clear. After transferring to a separatory funnel extracted with ether and water and then dried the ether layer with sodium sulfate. After removing the ether, 0.665 g of 38 was isolated. Isomer 37 could be obtained in a similar procedure.

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#### Example 23

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(3a, 4a, 5a) 3-Butyl-3-athyl-7-(n-harylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiopino-1,1-diamido (60) and (3a,6b,5b) 3-Butyl-3-othyl-7-(n-hozylamino)-4-hydroxy-5-phenyl-2,3,4,5-totrahydrobenzothiopino-1,1-dioxido (41)

Stop 1. 2-((2-Benzyl-4-(n-

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hexylamino)phonylsulfonyl)methyl)-2-othylbaxanal (39)

In a Fischer porter bottle weighed out 0.5 g of 34 (1.2 mwoles) and dissolved in 3.8 ml of ethanol under nitrogen. Next added 0.1 g of Pd/C and 3.8 ml of hexanal. Seal and pressure to 50 psi of hydrogen gas. Stirred for 48 h. After filtering off the catalyst and removing the solvent by rotary evaporation 39 was

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mobile phase to 70/30 hexane/ethyl acetate. The product hexane ethyl acetate and gradually increasing the was characterized by NMR and mass spectra. isolated by column chromatography (0.16 g) using 90/10

tetrahydrobenzothiepine-1,1-dioxide (41) hexylamino)-4-hydroxy-5-phenyl-2,3,4,5dioxide (40) and (3a,4b,5b) 3-Butyl-3-ethyl-7-(nhydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-Step 2. (3a,4a,5a) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-

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mg); 41(58.9 mg). mobile phase to 70/30 hexane/ethyl acetate. 40 ( 53.2 the two isomers 40 and 41. The two isomers were dried product (0.143 g) indicated only the presence of ml of chilled 10% HCl and stirred at -10 °C for 5 min. of a salt/water bath. Slowly add 0.113 g of potassium hexane ethyl acetate and gradually increasing the separated by silica gel chromatography using 90/10 ether. Dried over sodium sulfate. Proton NMR of the Transferred to a separatory funnel and extract with the two isomers 40 and 41 were observed. Next added 5 of the starting material was consumed by TLC and only tert butoxide (0.335 mmole). After 15 min at -10 °C all anhydrous THF under nitrogen. Cool to -10 °C by means charged with 0.158 g 39 (0.335 mmole) and 5 ml A 2-neck, 25 ml round bottomed flask with stir bar was

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#### xample 24

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## Quaternization of amine substrates 40 and 41

produces the dimethylhexylamino quaternary salt. methyl iodide in the presence of 2,6 dimethyl lutidine halides. For example 40 in DMF with 5 equivalents of alkylated to quaternary salts by reaction with alkyl Amine products such as 40 and 41 can be readily

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#### <u>Example 25</u>

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2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (42) (3a, 4b, 5b) 3-Butyl-3-ethyl-4-hydroxy-5-(4-iodophenyl)-

with 50 ml methylene chloride and washed with 10 ml of , 0.67 g of mercuric triflate were dissolved in 20 ml No. 17, pp 5139-5146 (1994) Bachki, F. Et al.Mass 1 M sodium thiosulfate; 10 ml of saturated KI; and Iodine was added and the solution was stirred at room of dry methylene chloride with stirring. Next 0.34 g of In a 25 ml round bottomed flask 0.5 g (1.3 mmole) of 6d a diiodide adduct. The mixture was separated by column spectrum indicated a mixture of 6d , mono iodide 42 and dried over sodium sulfate. See Tetrahedron, Vol.50, temperature for 30 h. The reaction was then diluted chromatography and 42 was characterized bt NMR and mass

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#### Example 26

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8 hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (3a,4b,5b) 3-Butyl-5-(4-carbomethoxyphenyl)-3-ethyl-4-

A 0.1 g sample of 42 ( 0.212 mmole), 2.5 ml dry toluene and 37 mg of palladium chloride (0.21 mmole) The product was characterized by NMR and mass spectra of product was isolated. overnight. The catalyst was filtered and a high yield carbon monoxide. The reaction was heated at 100 °C was charged to a glass lined mini reactor at 300 psi methanol, 38 µl triethylamine (0.275 mmole) , 0.3 ml

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Note the ester functionalized product 43 can be

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converted to the free acid by hydrolysis.

#### Example 27

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phony1-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (48), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-

methoxy-5-phenyl-2,3,4,5-tetrahydrobenxothiepine-1,1dioxide (49)

Step 1. 2-Mercapto-5-methoxybenzophenone (50)

in 600 ml cyclohexane according to the procedure in WO distilled to remove 4-methoxythiophenol and gave 43.86 93/16055 gave 73.2 g of brown oil which was kugelrohr Reaction of 66.2 g of 4-methoxythiophenol with 360 ml tetramethylethylenediamine and 66.7 g of benzonitrile of 2.5 N n-butyllithium, 105 g of g of crude 50 in the pot residue.

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Btep 2. 2-((2-Benroy1-4-methoxyphenylthio)methyl)-2ethylbexensl (51)

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procedure for the preparation of 2 gave 10.5 g of crude product which was purified by HPLC (5% ethyl acetate-Reaction of 10 g (0.04 mole) of crude 50 with 4.8 g triethylamine in 50 ml of diglyme according to the (0.02 mole) of mesylate 1 and 3.2 ml (0.23 mole) of hexane) to give 1.7 g (22%) of **51**.

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Step 3. 2-((2-Benroyl-4-methoxyphenylsulfonyl)methyl)-2-ethyl-bexanal (52)

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of 50-60% MCPBA according to the procedure of step 2 of methylene chloride was reacted with 2.0 g (6.2 mmoles) procedure A in example 18 gave 1.16 g (90%) of 52 as a A solution of 1.2 g (3.1 mmoles) of 51 in 25 ml of yellow oil.

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Btep 4. 2-((2-Bensyl-4-methoxyphenylsulfonyl)methyl)-2-ethylbexanal (53) Hydrogenation of 1.1 g of 52 according to the procedure of step 3 of procedure A of example 18 gave 53 as a yellow oil (1.1 g).

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Step 5. (3s,4s,5s) 3-Butyl-3-ethyl-4-hydroxy-7-methoxymethoxy-5-phenyl-2,3,4,5-tetrahydrobensothiepine-1,1-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (48), and (3a, 4b, 5b) 3-Butyl-3-ethyl-4-hydroxy-7dioxide (49)

mp 153-154 °C and 90 mg (8%) of 49 as solid, mp 136-140 butoxide and 25 ml of anhydrous THF was held at reflux example 18 to give 1.07 g of a crude product which was purified by HPLC to give 40 mg (4%) of 48 as crystals, for 2 h and worked up as in step 4 of procedure A of A solution of 1.1 g of 53, 0.36 g of potassium t-

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5-Phany1-2, 3-dihydrospirobenzothiepine-3, 1'-cyclohexans Example 28 57

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3tep 1. 1-(Hydroxymethyl)-cyclohexanecarboxaldehyda (24)

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was evaporated to remove methanol. The reaction mixture under vacuum to give 75 g (59.7%) of thick oil. Proton NMR and mass spectra were consistent with the product. brine, and dried over sodium sulfate and concentrated formaldehyde in 225 ml of methanol was added dropwise mixture was stirred at room temperature over 48 then 90 ml of 1 N Sodium hydroxide in 1 h. The reaction was diluted with water and extracted with methylene chloride. The organic layer was washed with water, To a cold (O'C' mixture of 100 g (0.891 mole) of cyclohexanecarboxaldehyde, 76.5 g of 37% of

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Step 2. 1-(mesyloxymethyl)cyclohexanecarboxaldehyde (22)

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and 65.29 g (0.57 mole) of methanesulfonyl chloride in To a cold (0°C' mixture of alcohol 54 (75 g, 0.54 mole) pyridine (47.96 g, 0.57 mole) in 40 ml of methylene 80 ml of methylene chloride was added a solution of

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chloride. The reaction mixture was stirred at room temperature for 18 h then quenched with water, acidified with conc. HCl and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 91.63 g (77.8%) of thick oil. Proton NMR and mass spectra were consistent with the product.

#### Stop 3. 1-((2-

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# Bonzoylphonylthio)methyl)cyclohoxanocarboxaldohyda (56)

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A mixture of 69 g (0.303 mole) of 2mercaptobenzophenone, 82 g (0.303 mole) of mesylate 55,
32 g of triethylamine, and 150 ml of diglyme was
stirred and held at reflux for 24 h. The mixture was
cooled, poured into dil. HCl and extracted with
methylene chloride. The organic layer was washed with
10% NaOH, water, brine, and dried over sodium sulfate
and concentrated under vacuum to remove excess diglyme.
This was purified by silica gel flush column (5% EtOAc:
Hexane) and gave 18.6 g (75.9%) of yellow oil. Proton
NMR and mass spectra were consistent with the product.

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# Step 4. 5-Phonyl-2,3-dihydrospirobenzothiepina-3,1'cyclobexane (57)

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To a mixture of 6.19 g of zinc dust and 100 ml of dry DME was added TiCl,(16.8 g, 0.108 mole). The reaction mixture was heated to reflux for 2 h. A solution of compound 56 (8.3 g, 0.023 mole) in 50 ml of DME was added dropwise to the reaction mixture in 1 h and the mixture was held at reflux for 18 h. The mixture was cooled, poured into water and extracted with ether. The organic layer was washed with water, brine, and dried over sodium sulfate, filtered through celite and concentrated under vacuum. The residue was purified by HPLC (10% EtOAc: Hexane) to give 4.6 g (64%) of white

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solid, mp 90-91 °C. Proton and carbon NMR and mass spectra were consistent with the product.

#### Example 22

8b-Phanyl-1a,2,3,8b-tetrahydrospiro(benzothiepino[4,5-b]oxirene-2,1'-cyclohexane)-4,4-dioxide (58)

To a solution of 57 (4.6 g, 15 mmole) in 50 ml chloroform under nitrogen was added 55% MCPBA (16.5 g, 52.6 mmole) portionwise with spatula. The reaction was held at reflux for 18 h and washed with 10% NaOH(3X), water, brine, and dried over sodium sulfate and concentrated under vacuum to give 5 g of crude product. This was recrystallized from Hexane/EtOAc to give 4.31 g (81%) of yellow solid, mp 154-155 °C. Proton and carbon NMR and mass spectra were consistent with the product.

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#### Example 30

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trans-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (59)

A mixture of 0.5 g (1.4 mmoles) of 58 , 20 ml of ethanol,10 ml of methylene chloride and 0.4 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 3 h at room temperature. The crude reaction slurry was filtered through Celite and evaporated to dryness. The residue was purified by HPLC (10% EtOAc-Hexane, 25% EtOAc-Hexane). The first fraction was 300 mg (60%) as a white solid, mp 99-100 °C. Proton NMR showed this was a trans isomer. The second fraction gave 200 mg of solid which was impure cis isomer.

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#### Example 31

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cis-é-Hydroxy-5-phenyl-2,3,é,5-tetrabydro
spiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (60)

To a solution of 0.2 g (0.56 mmole) of 59 in 20 ml of CH<sub>c</sub>Cl<sub>1</sub>, was added 8 g of 50% NaOH and one drop of Aliquat-136 (methyltricaprylylammonium chloride) phase transfer catalyst. The reaction mixture was stirred for 10 h at room temperature. Twenty g of ice was added to the mixture and the mixture was extracted with CH<sub>c</sub>Cl<sub>1</sub> (3x10 ml) washed with water, brine and dried over MgSO<sub>1</sub> and concentrated in vacuo to recover 0.15 g of crude product. This was recrystallized from Hexane/EtOAc to give 125 mg of white crystal, mp 209-210 °C. Proton and carbon NMR and mass spectra were consistent with the product.

#### Example 32

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(3a, 4a, Sa) 3-Butyl-3-othyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenrothiepine (61), and (3a,4b,5b) 3-Butyl-3-othyl-4-hydroxy-5-phonyl-2,3,4,5-tetrahydrobenrothiepine (62)

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To a solution of 0.5 g (1.47 mmole) of compound 47 in 5 ml of anhydrous THF was added 0.17 g (1.47 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred at room temperature for 18 h and quenched with 10 ml of 10% HCl. The organic was extracted into methylene chloride. The methylene chloride extract was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by HPLC (2% EtOAc-hexane) to give 47 mg of 61 in the second fraction and 38 mg of 61 in the third fraction. Proton NMR and mass spectra were consistent with the assigned structures.

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(3a, 4a, 5a) 3-Butyl-3ethyl-4-hydroxy-7-amino-5-phenyl2,3,4,5-tetrahydrobonzothlepine-1,1-dioxide (63) and
(3a, 4b, 5b) 3-Butyl-3-ethyl-4-hydroxy-7-amino-5-phenyl2,3,4,5-tetrahydrobenzothlepine-1,1-dioxide(64)

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An autoclave was charged with 200 mg of 37 in 40 cc ethanol and .02 g 10 % Pd/C. After purging with

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nitrogen the clave was charged with 100 psi hydrogen and heated to 55 C. The reaction was monitored by TLC and mass spec and allowed to proceed until all of 37 was consumed. After the reaction was complete the catalyst was filtered and the solvent was removed in vacuo and the only observable product was amine 63. This same procedure was used to produce 64 from 38.

#### Frample 14

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(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (65), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (66).

Alkylation of e-methoxyphenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-methoxybenzyl)phenol in 35% yield. This material was converted to compound 65, mp 138.5-141.5 °C, and compound 66, mp 115.5-117.5 °C, by the procedure similar to that in Example 18 method B.

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#### xample 35

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(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (67), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-(trifluoromethyl)phenyl)-2,3,4,5-

tetrahydrobenzothiepine-1,1-dioxide (68).
Alkylation of 4-methoxyphenol with 3-

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(trifluoromethyl)benzyl chloride according to the procedure described in J. Chem. Soc. 2431 (1958) gave 4-methoxy-2-(3'-(trifluoromethyl)benzyl)phenol. This material was converted to compound 67, mp 226.5-228 °C, and compound 68, mp 188-190°C, byu the procedure similar to that in Example 18 method B.

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#### Example 36

(3a, 4a, 5a) 3-Buty1-3-ethy1-5-(4'-fluoropheny1)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (69), and (3a,4b,5b) 3-Buty1-3-ethy1-5-(4'-fluoropheny1)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (70).

Alkylation of 4-methoxyphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc. 2431 (1958) gave 4-methoxy-2-(4'-fluorobenzyl)phenol. This material was converted to compound 69 and compound 70 by the procedure similar to that in Example 18 method B.

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#### Example 3

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(3a, 4a, 5a) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (71), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (72).

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Alkylation of 4-methoxyphenol with 3-fluorobenzyl chloride according to the procedure described in J. Chem. Soc. 2431 (1958) gave 4-methoxy-2-(3'-fluorobenzyl)phenol. This material was converted to compound 71 and compound 72 by the procedure similar to that in Example 18 method B.

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#### Example 38

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(3a, 4a, 5a) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (73), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (74).

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Alkylation of 4-methoxyphenol with 2-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(2'-fluorobenzyl)phenol. This material was converted to

compound 73 and compound 74 by the procedure similar to that in Example 18 method B.

#### Example 39

(3a,4a,5a) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (75), and (3a,4b,5b) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (76).

Alkylation of 4-bromophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-bromo-2-(3'-methoxybenzyl)phenol. This material was converted to compound 75, mp 97-101.5 °C, and compound 76, mp 102-106 °C, by the procedure similar to that in Example 18 method B.

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#### Example 40

20 (3a,4a,5a) 3-Butyl-3-ethyl-7-fluoro-5-(4'fluorophenyl)-4-hydroxy-2,3,4,5tetrahydrobenzothiepine-1,1-dioxide (77), and
(3a,4b,5b) 3-Butyl-3-ethyl-7-fluoro-5-(4'fluorophenyl)-4-hydroxy-2,3,4,5tetrahydrobenzothiepine-1,1-dioxide (78).

Alkylation of 4-fluorophenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(4'-fluorobenzyl)phenol. This material was converted to compound 77, mp 228-230 °C, and compound 78, mp 134.5-139 °C, by the procedure similar to that in Example 18 method B.

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#### Example 41

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(3a,4a,5a) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (79), and (3a,4b,5b) 3-Butyl-3-ethyl-7-fluoro-

tetrahydrobenzothiepine-1,1-dioxide (80). 40hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-

compound 79, as a solid and compound 80, mp 153-155 °C, methoxybenzyl)phenol. This material was converted to by the procedure similar to that in Example 18 method chloride according to the procedure described in J. Alkylation of 4-fluorophenol with 3-methoxybenzyl Chem. Soc, 2431 (1958) gave 4-fluoro-2-(3'-

#### Example 42

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hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-1,1-dioxide (81).

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first fraction was impure (3a,4a,5a) 3-butyl-3-ethyl-4reaction mixture was dilute with ether and washed with A mixture of 0.68 (1.66 mmol) of compound 77, 0.2 g (5 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at room temperature for 16 days. The purified by HPLC (20% ethyl acetate in hexanes). The The residue was hydroxy-7-methylthio-5-(4'-fluorophenyl)-2,3,4,5tetrahydrobenzothiepine-1,1-dioxide. The second water and brine and dried over M,SO,. The ether fraction was compound 81, mp 185-186.5 °C. solution was concentrated in vacuo.

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#### Example 43

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(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4tetrahydrobenzothiepine-1,1-dioxide (82) nydroxy-7-(1-pyrrolidiny1)-2,3,4,5-

reaction mixture was diluted with ether and washed with A mixture of 0.53 g (1.30 mmol) of compound 78 and 5 ml solution was concentrated in vacuo. The residue was water and brine and dried over M,SO,. The ether of pyrrolidine was held at reflux for 1 h.

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crystallized from ether-hexanes to give compound 82, mp 174.5-177 °C.

#### Example 44

(3a, 4b, 5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4tetrahydrobenzothiepine-1,1-dioxide (83) hydroxy-7-(1-morpholinyl)-2,3,4,5A mixture of 0.4 g (0.98 mmol) of compound 78 and 5.0 g ether (30 ml) and washed with water and brine and dried (56 mmol) of morpholine was held at reflux for 2 h and concentrated in vacuo. The residue was diluted with over M,SO,. The ether solution was concentrated in vacuo. The residue was recrystallized from etherhexanes to give compound 83, mp 176.5-187.5  $^{\circ}\text{C}.$ 

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#### Example 45

nydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1dioxide (84), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-(3a,4a,5a) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5tetrahydrobenzothiepine-1,1-dioxide (85).

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compound 84 and compound 85 by the procedure similar to fluorobenzyl)phenol). This material was converted to chloride according to the procedure described in J. Alkylation of 4-methylphenol with 4-fluorobenzyl Chem. Soc, 2431 (1958) gave 4-methyl-2-(4'that in Example 18 method B.

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#### Example 46

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hydroxyphenyl}-2,3,4,5-tetrahydrobenzothiepine-1,1-(3a,4b,5b) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'tetrahydrobenzothiepine-1,1-dioxide (86), and (3a, 4b, 5b) 3-Butyl-3-ethyl-4-hydroxy-5-(4'hydroxyphenyl) -7-methoxy-2,3,4,5dioxide (87).

To a solution of 0.52 (1.2 mmol) of compound 66 in 20 ml of methylene chloride was added 1.7 g (6.78 mmol) of born tribromide. The reaction mixture was cooled to -78 °C and was stirred for 4 min. An additional 0.3 ml of boron tribromide was added to the reaction mixture and the reaction mixture was stirred at -78 °C for 1 h and quenced with 2 N HCl. The organic was extracted into ether. The ether layer was washed with brine, dried over M<sub>4</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue (0.48 g) was purified by HPLC (30% ethyl acctate in hexanes). The first fraction was 0.11 g of compound 86 as a white solid, mp 171.5-173 °C. The second fraction was crystallized from chloroform to give 0.04 g of compound 87 as a white solid, mp 264 °C (dec).

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#### Example 47

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(3a,4b,5b) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (88).

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Reaction of compound 70 with excess boron tribromide at room temperature and worked up as in Example 46 gave compound 88 after an HPLC purification.

#### Example 48

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(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-azetidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (89).

3

A mixture of 0.20 g (0.49 mmol) of compound 78, and 2.0 g (35 mmol) of aztidine was held at reflux for 3 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over MgSO4: The ether solution was concentrated on a steam bath. The separated crystals were filtered to give 0.136 g of 89 as prisms, mp 196.5-199.5 °C.

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#### Example 49

(3a,4a,5a) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (90). (3a,4b,5b) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (91).

A mixture of 0.4 g (0.95 mmol) of compound 79, 0.08 g (1.14 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at 60 °C for 2 h. An additional 1.4 mmol of sodium methanethiolate was added to the reaction mixture and the mixture was stirred at 60 °C for an additional 2 h. The reaction mixture was triturated with 100 ml of water and extracted methylene chloride. The methylene chloride water mixture was filtered through Celite and the methylene chloride layer was dried over M<sub>2</sub>SO, and concentrated in vacuo. The first fraction (0.1 g) was compound 90, mp 117-121 °C. The second fraction (0.16 g) was compound 91, mp 68-76 °C.

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Example 50

Preparation of polyethyleneglycol functionalized benzothiepine A.

A 50 ml rb flash under a nitrogen atmospherewas charged with 0.54 g of M-Tres-5000 (Polyethyleneglycol 10 Tresylate [methoxy-PEG-Tres, MW 5000] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.055 g Compound No. 136, 0.326 C,CO, and 2cc anhydrous acetonitrile. The reaction was stirred at 30 C for 5 days and then the solution was

15 filtered to remove salts. Next, the acetonitrile was removed under vacuum and the product was dissolved in THF and then precipitated by addition of hexane. The polymer precipitate was isolate by filtration from the solvent mixture (THF/hexane). This precipitation procedure was continued until no Compound No. 136 was detected in the precipitated product (by TLC SiO2). Next, the polymer precipitate was dissolved in water and filtered and the water soluble polymer was dialyzed for 48 hours through a cellulose dialysis tube (Spectrum® 7,45 mm x 0.5 ft, cutoff 1.000 MW). The polymer solution was then removed from the

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chromatography indicated the presence of a 4500 MW polymer and also verified that no free Compound No. 136 was present. This material was active in the IBAT in vitro cell assay.

Example 51

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Preparation of Compound 140

No. 140

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No. 111

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A 2-necked 50 ml round bottom Flask was charged with 0.42g of Tres-3400 (Polyethyleneglycol Tresylate [Tres-PEG-Tres, MW 3400] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.1 potassium carbonate, 0.100g of Compound No. 111 and 5 ml anhydrous DMF. Stir for 6 days at 27 °C. TLC indicated the disappearance of the starting

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consistent with the desired product & and gel permeation

dialysis tube and lyophilized until dried. The NMR was

until dried 0.341 g). NMR was consistent with the  $\times$  0.5 ft, cutoff 1,000 MW). The polymer solution was chloride and then extracted with water. then removed from the dialysis tube and lyophilized °C through a cellulose dialysis tube (spectrum® 7 ,45mm dissolved in water and then dialyzed for 48 hours at 40 evaporator. Dry wgt. 0.4875 g. Next, the polymer was separatory funnel and diluted with 50 cc methylene Compound No. 111. The solution was transferred to a desired product B. layer was evaporated to dryness by means of a rotary The organic

#### Example 52

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No. 134

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on a silica gel column using 80/20 hexane ethyl and the desired product Compound No. 134 was isolated temperature and then worked up by washing with 10 cc DMF. The reaction was stirred for 4 days at room 0.6g (1.5 mmoles) of 1,2-bis-(2-iodoethoxy)-ethane and A 10 cc vial was charged with 0.21 g of Compound No. 136 (0.5mmoles), 0.17g (1.3 mmoles)potassium carbonate, The ether layer was stripped to dryness

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#### Example 53

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#### Example 54

No. 112

No. 113

chromatographed on Silicage (80/20 ethyl consumed and the reaction was cooled to room nitogen. Next, the reaction was slowly heated to 40 of 1,2-Bis [2-iodoethoxylethane] at 10 °C under 0.055g of 60% NaH dispersion and 0.230g (0.62 mmoles) 0.5g (1.24mmoles) of 69462, 13 mls of anhydrous DMF, A two necked 25 ml round bottom Flask was charged with °C. After 14 hours all of the Compound No. 113 was layer was evaporated to dryness and then temperature and extracted with ether/water. The ether

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acetate/hexane). Isolated Compound No. 112 (0.28 g) was characterized by NMR and mass spec.

Example 55

No. 135

In a 50 ml round bottom Flask, add 0.7g (1.8 mmoles) of Compound No. 136, 0.621g of potassium carbonate, 6 ml DMF, and 0.33g of 1,2-Bis [2-iodoethoxylethane]. Stir at 40 °C under nitrogen for 12 hours. The workup and isolation was the same procedure for Compound No. 112.

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# Examples 56 and 57 (Compound Nos. 131 and 137)

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The compositions of these compounds are shown in Table  $\bf 3$ 

The same procedure as for Example 55 except appropriate benzothiepine was used.

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### Example 58 (Compound No. 139)

The composition of this compound is shown in Table 3.

Same procedure as for Example 55 with appropriate
benzothiepine 1,6 dilodohexane was used instead of 1,2Bis [2-iodoethoxylethane].

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Example 59 (Compound No. 101)

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This compound is prepared by condensing the 7-NH, benzothiepine with the 1,12-dodecane dicarboxylic acid or acid halide.

Example 60 (Compound No. 104)

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No. 104

substituted amino derivatives of this invention Compound No. 104. with potassium t-butoxide yields a mixture of dimethylamine derivative XXVIII. Cyclization of XXVII sulfone-aldehyde XKV formaldehyde and 100 psi hydrogen and 55 C for 12 hours catalyzed by palladium on carbon sulfone-aldehyde XXIV (see Scheme 5). Reduction of the Oxidation of XXIII with 2 equivalents of MCPBA yields sulfide with mesylate IV gives sulfide-aldehyde XXIII. in the same reaction vessel yields the substituted chloro-4-nitrodiphenylmethane 32. Reaction of 32 with lithium sulfide followed by reacting the resulting triethylsilane and trifluoromethane sulfonic acid to 2-2-Chloro-4-nitrobenzophenone is reduced with

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Scheme 6

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Example 61

No. 102

A 1 oz. Fisher-porter bottle was charged with 0.14 g precipitating with diethyl ether. iodide, and 7 ml of anhydrous acetonitrile. Heat to 50 isolated by concentrating to 1 cc acetonitrile and then °C for 4 days. The quat. Salt Compound No. 192 was (0.34 mmoles) of 70112, 0.97 gms (6.8 mmoles) of methyl

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15 Example 62

No. 125

bubbled through the solution for 5 minutes at 0  $^{\circ}\mathrm{C}$  and reaction was stirred overnight and the desired product was isolated by removing solvent by rotary evaporation. A 0.1 g (0.159 mmoles) sample of Compound No. 134 was Fischer-porter bottle and then trimethylamine was dissolved in 15 ml of anhydrous acetonitrile in a then capped and warmed to room temperature. The

### Example 63 (Compound No. 295)

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No. 113

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acetonitrile at 0 °C was reacted with 0.248 mmoles (.10 g) of Compound No. 54 in 2.5cc of acetonitrile at 0  $^{\circ}$ C. iodoethoxylethane]. After warming to room temperature, The product was isolated by column Sodium Hydride 60% (11 mg, 0.27 mmoles) in 1 cc of Next, 0.(980g 2.48 mmoles) of 1,2-Bis [2stir for 14 hours.

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chromatography.

No. 286

Following a procedure similar to the one described in Example 86, infra (see Compound No. 118), the title solid; mp 180-181 °C; 'H NMR (CHC1,) d 0.85 (t, J=61.46-1.56 (m, 1H), 1.64-1.80 (m, 1H), 2.24-2.38 (m, iz, 3H\_, 0.92 (t, J = 6 Hz, 3H), 1.24-1.42 (m, 2H), compound was prepared and purified as a colorless

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1H), 8.06 (d, J = 8 Hz, 1H). FABMS m/z 494 (M+H), HRMS calcd for (M+H) 494.2001, found 494.1993. Anal. Calcd. 1H), 3.15 (AB,  $J_{AB}$  = 15 Hz,  $D_V$  = 42 Hz, 2H), 4.20 (d, J = 8 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.46 (s, 1H), 6.68 (s, 1H), 7.29-7.51 (m, 10H), 7.74 (d, J = 8 Hz, for C,H,NO,S: C, 68.13; H, 6.33; N, 2.84. Found: C, 68.19; H, 6.56; N, 2.74.

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No. 295

### Example 65 (Compound No. 287)

·1H), 1.32-1.42 (m, 1H), 1.48-1.60 (m, 1H), 1.64-1.80 7.53 (m, 5H), 7.88 (d, J = 8 Hz, 1H); ESMS 366 (M+L1). (s, 1H), 5.95 (s, 1H), 6.54 (d, J = 7 Hz, 1H), 7.29-Hz, 3H), 0.92 (t, J = 6 Hz, 3H), 1.28, (d, J = 8 Hz, solid: mp 245-246 °C, 'H NMR (CDC1) d 0.84 (t, J = 6compound was prepared and purified as a colorless Found: C, 66.54; H, 7.20; N, 3.69. Anal. Calcd. for C,H,NO,S: C, 66.82; H, 7.01; N, 3.90 42 Hz, 2H), 3.97 (bs, 2H), 4.15 (d, J = 8 Hz, 1H), 5.49 (m, 1H), 2.20-2.36 (m, 1H), 3.09 (AB,  $J_{M} = 15 \text{ Hz}$ ,  $D_{V} =$ in Example 89, infra (see Compound No. 121), the title Following a procedure similar to the one described

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### Example 66 (Compound No. 288)

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5.97 (s, 1H), 6.56 (dd, J = 2.1, 8.4 Hz, 1H), 7.31-7.52 = 15 Hz, 1H), 4.00 (s, 1H), 5.30 (s, 1H), 5.51 (s, 1H), 3H), 1.49 (s, 3H), 3.00 (d, J = 15 Hz, 1H), 3.28 (d, Jcolorless solid: mp 185-186°C; 'H NMR (CDC1,) d1.12 (s. chromatography to give the desired product as a compound was prepared and purified by silica gel in Example 89, infra (see Compound No. 121), the title (m, 5H), 7.89 (d, J = 8.4 Hz, 1H). MS (FAB+) (M+H) m/zFollowing a procedure similar to the one described

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### Example 67 (Compound No. 289)

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solid: mp 205-206 °C; 'H NMR (CDC1,) d 0.80-0.95 (m, 2.2, 1H), 6.54 (dd, J = 8.5, 2.2 Hz, 1H), 7.28-7.50 (m Hz, 2H), 3.15 (d, J = 15.1 Hz, 2H), 3.96 (s, br, 2H), 6H), 1.10-1.70 (m, 7H), 2.15 (m, 1H), 3.02 (d, J = 15.3chromatography to give the desired product as a white compound was prepared and purified by silica gel in Example 89 (see Compound No. 121), the title 6H), 7.87 (d, J = 8.5 Hz, 1H). MS (FAB): m/z 388 (M+H) 4.14 (d, J = 7.8 Hz, 1H), 5.51 (s, 1H), 5.94 (d, J =Following a procedure similar to the one described

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### Example 68 (Compound No. 290)

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No. 290

Following a procedure similar to the one described in Example 89, infra (see Compound No. 121), the title compound was prepared and purified as a colorless. solid: mp = 96-98 °C, 'H NMR (CDC1,) d 0.92 (t, J = 7 Hz, 6H), 1.03-1.70 (m, 11H), 2.21 (t, J = 8 Hz, 1H), 3.09 (AB,  $J_{ss} = -18$  Hz, Dv = 38 Hz, 2H), 3.96 (bs, 2H), 4.14 (d, J = 7 Hz, 1H), 5.51 (s, 1H), 5.94 (s, 1H), 6.56 (d, J = 9 Hz, 1H), 7.41-7.53 (m, 6H), 7.87 (d, J = 8 Hz, 1H); FABMS m/z 416 (M+H).

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Example 69

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Following a procedure similar to the one described in Example 86, infra (see Compound No. 118), the title compound was prepared and purified as a colorless solid:  $^{1}H$  NWR (CDC1,) d 0.91 (t, J=7 Hz, 6H), 1.02-1.52 (m, 11H), 1.60-1.70 (m, 1H), 2.23 (t, J=8 Hz,

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1H), 3.12 (AB, J<sub>M</sub> = 18 Hz, Dv = 36 Hz, 2H), 4.18 (d, J = 7 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.43 (s, 1H), 6.65 (s, 1H), 7.29-7.52 (m, 10H), 7.74 (d, J = 9 Hz, 1H), 8.03 (d, J = 8 Hz, 1H); ESMS m/z 556 (M+Li).

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6 Hz, 2H), 7.87 (d, J = 9 Hz, 1H). 2H), 4.09 (bs, 2H), 5.49 (s, 1H), 5.91 (s, 1H), 6.55 (d, J = 9 Hz, 1H), 7.10 (t, J = 7 Hz, 2H), 7.46 (t, J = 9 Hz, 2H)Hz, 6H), 1.03-1.50 (m, 10H), 1.55-1.70 (m, 2H), 2.18 solid: mp = 111-112.5°C, 'H NMR (CDC1,) d 0.90 (t, J = 8compound was prepared and purified as a colorless (t, J = 12 Hz, 2H), 3.07 (AB,  $J_{ab} = 15 \text{ Hz}$ ,  $D_V = 45 \text{ Hz}$ , in Example 89, infra (see Compound No. 121), the title Pollowing a procedure similar to the one descried

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Example 71 (Compound No. 293)

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No. 293

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Compound No. 291 using BBr,, the title compound was During the preparation of Compound No. 290 from

J = 9 Hz, 1H), 7.12 (d, J = 8 Hz, 2H), 7.16-7.26 (m, 1H), 4.12 (s, 1H), 5.44 (s, 1H), 5.84 (s, 1H), 6.42 (d. 1H), 3.04 (AB,  $J_{10} = 15 \text{ Hz}$ , DV = 41 Hz, 2H), 4.08 (8, 1.60 (m, 10H), 1.50-1.66 (m, 2H), 2.16 (t, J = 8 Hz, isolated:  ${}^{1}H$  NMR (CDC1) d 0.85 (t, J = 6 Hz, 6H), 0.98-10H), 7.83 (d, J = 8 Hz, 1H); ESMS m/z 512 (M+Li).

### Example 72 (Compound No. 294)

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was prepared and purified as a colorless solid: 1H NMR 1H), 7.27-7.42 (m, 4H), 7.45 (d, J=8 Hz, 2H), 7.876H), 3.05 (AB,  $J_{M} = 15$  Hz, DV = 42 Hz; 2H), 4.05-4.18 1.60-1.70 (m, 1H), 2.24 (t, J=8 Hz, 1H), 2.80 (s, in Example 60 (Compound No. 104), the title compound (m, 2H), 5.53 (s, 1H), 5.93 (s, 1H), 6.94 (d, J = 9 Hz)(CDC1,) d 0.90 (t, J = 6 Hz, 6H), 1.05-1.54 (m, 9H), (d, J = 9 Hz, 1H); ESMS m/z 444 (M+H). Structures of the compounds of Examples 33 to 72 Following a procedure similar to the one described

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are shown in Tables 3 and 3A.

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## Examples 73-79, 87, 88 and 91-102

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prepared having the structures set forth in Table 3 the substituents to be introduced, compounds were described in those of Examples 1 to 72 appropriate to position on the benzo ring (R). to introduce the indicated substituents in the 4- and principles of organic synthesis well known to the art The starting materials illustrated in the reaction 5- positions (R', R', R', R') and in the indicated schemes shown above were varied in accordance with Using in each instance a method generally

Structures of the the compounds produced in Examples 73-102 are set forth in Tables 3 and 3A.

Examples 80-84

Preparation of 4-chloro-3-[4-methoxy-Preparation of 115, 116, 111, 113 phenylmethyl]-nitrobenzene.

phosphorus pentachloride (0.328 mole 1.1 eq). Add 50 In a 500 ml 2-necked rb flask weigh out 68.3 gms nitrobenzoic acid (0.298 mole). Stir at room temp mls chlorobenzene. Slowly add 60 gms 2-chloro-5overnight under N2 then heat 1 hr at 50C.

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Remove chlorobenzene by high vacuum. Wash residue with hexane. Dry wt=55.5 gms.

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In the same rb flask, dissolve acid chloride (55.5 g 0.25 mole) from above with 100 mls anisole (about 3.4 eq). Chill solution with ice bath while purging with Slowly add 40.3g aluminum chloride (1.2 eq 0.3 mole). Stir under N, for 24 hrs.

After 24 hrs, the solution was poured into 300 mls layer once with 2% aqueous NaOH then twice with water. Dry organic layer with MgSO4, dry on vac line. Solid drying. Wt=34.57g (mixture of meta, ortho and para). 1N HCl soln. (cold). Stir this for 15 min. Extract several times with diethyl ether. Extract organic is washed well with ether and then ethanol before

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arm and par	found	57.45	5.51	8.8	12.16
בייים מיים מיים מיים מיים מיים מיים	theory	57.65	3.46	4.8	12.15
	Elemental	υ	×	Z	ប

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with trifluoromethane sulfonic aid and triethyl silane, crystallization with ethyl acetate/hexane affords pure With the next step of the reduction of the ketone 4-chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene.

and 118 from 2-chloro-4-nitrophenylmethane. From these 111 and 113 can be synthesized from the procedure used 4-Chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene Compounds was then reacted as specified in the synthesis of 117 procedures 115 and 116 can be synthesized. to prepare compound 121.

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Compound 114 can be prepared by reaction of 116 with ethyl mercaptan and aluminum trichloride.

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### Examples 85 and 86

Preparation of 117 and 118

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triethylsilane and trifluoromethane sulfonic acid to 2equivalents of MCPBA yields sulfone-aldehyde XXIV (see chloro-4-nitrodiphenylmethane 32. Reaction of 32 with sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields lithium sulfide followed by reacting the resulting sulfone-aldehyde XXIII. Oxidation of XXIII with 2 2-Chloro-4-nitrobenzophenone is reduced with Scheme 5).

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chloroformate (27.4g) in toluene in the presence of 35 ml toluene and 100 ml of ethanol and 3.2 g of 10% Pd/C catalyst. The amine product (.076 moles, 29.5 g) from and heated to 55 C and 100 psi of hydrogen gas for 14 ethanol/toluene and placed in a parr reactor with 100 hours. The reaction was then filtered to remove the The sulfone-aldehyde (31.8 g) was dissolved in g of potassium carbonate and stirred at room this reaction was then reacted with benzyl

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temperature overnight. After work up by extraction with water, the CB2 protected amine product was further purified by precipitation from toluene/hexane.

The CBZ protected amine product was then reacted with 3 equivalents of potassium t-butoxide in THF at 0 C to yield compounds 117 and 118 which were separated by silica gel column chromatography.

### Examples 89 and 90

Preparation of 121 or 122

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Compound 118 (.013 moles, 6.79g) is dissolved in 135 ml of dry chloroform and cooled to -78 C, next 1.85 ml of boron tribromide (4.9 g) was added and the reaction is allowed to warm to room temperature.

Reaction is complete after 1.5 hours. The reaction is quenched by addition of 10% potassium carbonate at 0 C and extract with ether. Removal of ether yields compound 121. A similar procedure can be used to produce 122 from 117.

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#### Examples 93-96

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Compounds 126, 127, 128 and 129 as set forth in Table 3 were prepared substantially in the manner described above for compounds 115, 116, 111 and 113, respectively, except that fluorobenzene was used as a starting material in place of anisole.

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TABLE 3
Specific compounds (#102-111,113-130,132-134,136,138,142-144,262-296)

Cpê         R¹         R²         R³         R³         R\$         (R³)q           102         Et-         n-Bu-         HO-         H-         Ph-         H-         I-, 7-           103         n-Bu-         Et-         HO-         H-         Ph-         H-         (CH3)3N+-           104         Et-         n-Bu-         HO-         H-         Ph-         H-         7-(CH3)2N+-           105         Et-         n-Bu-         HO-         H-         Ph-         H-         7-(CH3)2N+-           106         Et-         n-Bu-         HO-         H-         Ph-         H-         CH3502NH-           107         n-Bu-         Et-         HO-         H-         Ph-         H-         CH3502NH-           108         Et-         n-Bu-         HO-         H-         Pn-C10H21-         H-         7-NH2-           110         Et-         n-Bu-         HO-         H-         Pn-C10H21-         H-         7-NH2-           111         n-Bu-         Et-         HO-         H-         P-HO-Ph-         H-         7-NH2-           113         Et-         n-Bu-         HO-         H-         p-CH3O									
R1     R2     R3     R4     R5     R6       Et-     n-Bu-     HO-     H-     Ph-     H-       n-Bu-     Et-     n-Bu-     HO-     H-     Ph-     H-       Et-     n-Bu-     HO-     H-     P-n-CloH21-     H-       Et-     n-Bu-     HO-     H-     P-n-CloH21-     H-       Et-     n-Bu-     HO-     H-     P-HO-Ph-     H-       Et-     n-Bu-     HO-     H-     P-CH3O-Ph-     H-       Et-     n-Bu-     HO-     H-     P-CH3O-Ph-     H-	7-NH-CBZ	Ħ	p-CH30-Ph-	Ħ	Ä	ก-8u-	Et-	116	84
R1     R2     R3     R4     R5     R6       Et-     n-Bu-     H0-     H-     Ph-     H-       n-Bu-     Et-     n-Bu-     H0-     H-     Ph-     H-       Et-     n-Bu-     H0-     H-     P-H0-Ph-     H-	7-NH-CBZ	Γ	p-CH30-Ph-	Ħ	Ö	Et.	n-Bu-	115	83
R1     R2     R3     R4     R5     R6       Et-     n-Bu-     H0-     H-     Ph-     H-       n-Bu-     Et-     n-Bu-     H0-     H-     Ph-     H-       Et-     n-Bu-     H0-     H-     P-H0-Ph-     H-       Et-     n-Bu-     H0-     H-     P-H0-Ph-     H-	7-NH2-	Ħ	p-CH30-Ph-	#-	<b>B</b> O-	n-Bu-	Et-	114	82
R1     R2     R3     R4     R5     R6       Et-     n-Bu-     HO-     H-     Ph-     H-       H-     HO-     HO-     HO-     HO-     HO-     HO-       H-     Ph-     <	7-NH <sub>2</sub> -	Ŧ	p-80-Ph-	ä	ë	ก-8u-	Et-	113	82
R1     R2     R3     R4     R5     R6       Et-     n-Bu-     H0-     H-     Ph-     H-       n-Bu-     Et-     n-Bu-     H0-     H-     Ph-     H-									
R1     R2     R3     R4     R5     R6       Et-     n-Bu-     HO-     H-     Ph-     H-       n-Bu-     Et-     n-Bu-     HO-     H-     Ph-     H-	7-NH2-	Ŧ	p-80-ph-	F	节	Mt-	n-Bu-	111	80
R1 R2 R3 R4 R5 R6  Et- n-Bu- HO- H- Ph- H-  -O-Ph- H-  Et- n-Bu- HO- H- P-n-C10H21- H-  -O-Ph-	7-CH3CONH-	#	Ph-	Ħ	Ö	ก-8น-	Et-	110	79
R1 R2 R3 R4 R5 R6  Et- n-Bu- HO- H- Ph- H-	7-NH <sub>2</sub> -	Ħ	p-n-C <sub>10</sub> H <sub>21</sub> - -0-Ph-	Ŧ	P	n-Bu-	M ct	109	78
R1 R2 R3 R4 R5 R6  Et- n-Bu- HO- H- Ph- H-  -O-Ph-	7- C5H11CONH-	#	Ph-	Ħ	Ą	ก-ฮิบ-	Et-	108	77
R1 R2 R3 R4 R5 R6 Et- n-Bu- HO- H- Ph- H- Et- n-Bu- HO- H- Ph- H- Et- n-Bu- HO- H- Ph- H- Et- n-Bu- HO- H- Ph- H-	7-NH2-	Ħ	p-n-C10H21- -0-ph-	<b>#</b>	HO-	Et-	n-3u-	107	76
R1 R2 R3 R4 R5 R6 Et- n-Bu- HO- H- Ph- H- Et- n-Bu- HO- H- Ph- H- Et- n-Bu- HO- H- Ph- H- Et- n-Bu- HO- H- Ph- H-	7-Br-CH2- CONE-	<b>#</b>	<b>Ph-</b>	Ħ	HO-	n-Bu-	m t	106	75
R1 R2 R3 R4 R5 R6 Et- n-Bu- HO- H- Ph- H- Et- n-Bu- HO- H- Ph- H-	7- CH3SO2NH-	Ħ,	ph-	Ŧ	<b>H</b> O-	n-Bu-	E C	105	74
R1 R2 R3 R4 R5 R6 Et- n-Bu- H0- H- Ph- H- n-Bu- Et- H0- H- Ph- H-	7- (CH <sub>3</sub> ) 2N-	Ħ	Ph-	Ħ	P	n-Bu-	Et	104	6
R1 R2 R3 R4 R5 R6 Et- n-Bu- H0- H- Ph- H-	I", 7- (CH3) 3NT-	Ħ	Ph-	F	Š.	Et-	n-Bu-	103	73
21 22 13 24 15 R6	I-, 7- (CH <sub>3</sub> ) <sub>3</sub> N+-	Ħ	Ph-	7	HO	ก-ชิบ-	ř	102	61
	(R <sup>≭</sup> ) q	Re	R5	7	23	N2	N <sub>1</sub>	င္မွန္	×

PCT/US97/04076	8- CH3CO2-	J-Ph- 7-CH3S-		- 7-(N)- &zetidine	- 7-CH3O-		- 7-CB30-  -Ph- 7-CB30-		- 7-CH30-	- 7-CH30-	-Ph- 7-CH30-	- 7-EO-	7-85-	0-Ph- 7-Br-	-Ph- 7-F-	- 1-F-	m-CH30-Ph- 7-F-	- 7-E-	- 7-CH <sub>3</sub> O-	o-F-Ph- 7-CH30-	m-F-Ph- 7-CH30-	
	-N -ua	н- м-Сн30-Рh-	п-СИ30-Рh- н-	-F-Ph- H-	п-Сизо-Ра- н-	Ē	m-CF3-Ph- H- H- m-CF3-Ph-	m-E0-Ph- E-	m-20-Ph-	p-:-ph-	-44-7-q -#	p-5-Ph-	m-CH3O-Ph- H-	н- п-Сизо-рь-	H- p-7-Ph-	p-7-Ph- H-	H- m-CH3	m-CH30-Ph- H-	m-F-Ph- H-	H- 0-F	H- B-F	254
WO 97/33882	138 n-Bu- Et- EO- H-	90 Et- n-Bu- H- HO-	91 Et- n-Bu- EO- E-	89 Et- n-Bu- HO- H-	66 Et- n-Bu- HO- H-	Et- n-Bu- H-	68 Et- n-Bu- HO- K- 67 Et- n-Bu- H- HO-	87 Et- n-Bu- HO- H-	86 Et- n-Bu- HO- H-	70 Et- n-Bu- RO- H-	69 Et- n-Bu- 'R- HO-	88 Et- n-Bu- HO- H-	76 Et- n-Bu- HO- H-	75 Et- n-Bu- H- HO-	77 Et- n-Bu- H- HO-	78 Et- n-Bu- HO- H-	79 Et- n-Bu- H- RO-	80 Et- n-Bu- HO- H-	72 Et- n-Bu- HO- H-	73 Et- n-Bu- H- HO-	71 Et- n-Bu- H- HO-	
PCT/US97/04076	7-NB-CBZ 7-NR-CBZ 101		7-NACO2-t- 49 Bu	7-NH2-	, <b>~</b>	7-n-C <sub>6</sub> H <sub>13</sub> - NK-		CH2CH2O) 3- 46		7-NH2- 36	-		I -, -8- 39 (CH <sub>3</sub> ) <sub>3N</sub> + 39	C6H12O- 39	40	8-phthal- imidyl-		8-n-C10H21- 41	8- I- (C2H4O) 3-	86	8- HO-	
WO 97/33882	117 n-Bu- Et- HO- H- Ph- H- 118 Et- n-Bu- HO- H- Ph- H-	Et- n-Bu- HO- H- Ph-	120 n-Bu- Et- HO- H- Ph H-	121 Et- n-Bu- RO- R- Ph- H- H- 122 n-Bu- Et- : RO- H- Ph- H-	Et- n-Bu- HO- H- Ph-	124 n-Bu- Et- HO- H- Ph- H-	125 Et- n-Bu- HO- H- Ph4: H-		n-Bu- Et- RO- H- p-F-Ph-	n-Bu~ Et- HO- H- p-F-Ph-	R- p-F-Ph-	-u2-1-d -u-ng-u-ng-u-ng-u-ng-u-ng-u-ng-u-ng-u-n	130 Et- n-Bu- HO- H- Ph H-			132 Et- n-Bu- HO- H- Ph- H-	;	Et- n-Bu- RO- H-	134 Et- n-Bu- RO- R- Ph- R-		136 Et- n-Bu- HO- H- Ph- H-	Este
	88 85	6 83	20 20	& &	76	92	62	;	S 3		ς <del>χ</del>	3 3	<u>,</u>		8	g X	8	r :	25		100	

TABLE 3A Bridged Benzothiephenes (#101,112,131,135,137,139-141)

CPD #101 (Ex. 59)

2	,	೭	72	71	70	69	88	67	. 6	G	2	t		: 5	ŝ	42	8
296		295	294	293	292	291	290	289	288	287	286	. 82		<b>.</b> 22	85	81	74
Et.		L.	ก-ซิน-	n-Bu-	ก-ชิน-	ก-9น-	n-Bu-	n- C3H7-	CH3-	Et-	Et -	Et-	td (†	Et-	Et-	Et-	Et-
ก-8บ-		1 - BC -	n-Bu-	ח-80-	ก-ฮิน-	n-Bu-	n-Bu-	n- C3H7-	CH3-	Et-	-13 E	n-Bu-	n~Bu-	n-Bu-	n-Bu-	n-Bu-	ก-ฮิบ-
		Ö	ë P	Ö	HO-	ë	Ö	ĕ	Ö	Ģ	. <b>P</b>	ş	P P	'n	ĕ	Ö	ë ë
in:	. :	ï	ï	iii	æ	m	<b>#</b>	Ŧ	i;	m	Ŧ	Ŧ	Ħ	P	ij	Ŧ	Ħ
I", p- (CH <sub>3</sub> ) 3N+ (C <sub>2</sub> H <sub>4</sub> O) 3-Ph-	(C2H4O) 3-	0-I-	Ph-	Ph-	p-F-Ph-	Ph-	Ph-	₽h-	Ph-	Ph-	Ph-	p-8-84-	p-F-Ph-	<b>#</b>	p-F-Ph-	p-F-Ph-	0-2-bp-
#	7	F	Ħ	#	E I	7	<b>#</b>	III  -1	Ħ	æ:	Ħ	Ħ	۳	p-f-Ph-	Ħ	H	Ŧ
7-NH2-	\=\\#2-	7-1111	7- (CH <sub>3</sub> ) <sub>2</sub> N-	7-PhCH2N-	7-NH <sub>2</sub> -	7-NH-CBZ	7-NH <sub>2</sub> -	7-NH <sub>2</sub> -	7-NH <sub>2</sub> -	7-NH <sub>2</sub> -	7-NH-CBZ	7-(N)- pyrroli- dine	7-(N)- morpholine.	7-CH3-	7-CH3-	7-CH <sub>3</sub> S-	7-сн30-

CPD #131 (Ex. 56)

256

XX

(Ex. 21)

CPD #140

O-polyethyleneglycol-O

CPD #135 (Ex. 55)

(g. %)

CPD #137 (Ex. 57)

258

CPD #139 (Ex. 58)

**ል**\$ት

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#### Examples 104-231

on the benzo ring  $(R^*)$ . structures set forth in Table 4. The starting positions (R', R', R', R') and in the indicated position organic synthesis well known to the art in order to above are varied in accordance with principles of materials illustrated in the reaction schemes shown to the art, compounds are prepared having the necessary other common synthesis expedients well known the substituents to be introduced, including where described in those of Examples 1 to 72 appropriate to introduce the indicated substituents in the 4- and 5-Using in each instance a method generally

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TABLE 4
Alternative compounds #1 (#302-312, 314-430)

319	318	317	316	315	314	316	311	310	309	308	307	306	305	304	303	302	Cpd#
m-CH3O-Ph-	m-CH3O-Ph-	m-CH3O-Ph-	m-CH3O-Ph-	m-CH3O-Ph-	m-CH3O-Ph	ស- ស- ស-	p-F-Ph-	pードーPh~	p-F-Ph-	p-F-Ph-	p-F-Ph-	p-E-Ph-	p-E-Ph-	p-7-Ph-	p-F-Ph-	p-F-ph-	X5
7-PhS-	7-CH3S (0) 2-	7-CH3S (O)-	7-Ets-	7-(l-aziridine)	7-(1-azetidine)	7-(1-pyrazole)-	7-t-Bu-	7-192-	7-Et-	7-CH3O- 9-CH3O-	7-CH <sub>3</sub> S- 9-CH <sub>3</sub> S-	7-PhS	7-CH <sub>3</sub> S (0) <sub>2</sub> -	7-CH <sub>3</sub> S(O)-	7-EtS-	7-(1-aziridine)	(R*) q

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7-(N-pyrrolidine) 9-CH3S- 7-(CH3)2N- 9-CH3S- 7-(CH3)2N- 7-(N-M-CH2)2N- 7-CYClopropy1 7-(CH3)2N- 7-(N-aretidine 9-CH3S- 7-(N-pyrrolidine)- 9-CH3S- 7-(CH3)2N- 9-CH3S- 7-(CH3)2N- 9-CH3S- 7-(CH3)2N- 9-CH3S- 7-(CH3)2N- 9-CH3S- 7-(CH3)2N- 9-CH3S-	m-CH3O-Ph- m-CH3O-Ph- m-CH3O-Ph- m-CH3O-Ph- m-CH3O-Ph-	348 349 351 352 353		7-CH <sub>3</sub> S (0) 2- 9-CH <sub>3</sub> - 9-CH <sub>3</sub> - 7-CH <sub>3</sub> S- 9-CH <sub>3</sub> - 7-CH <sub>3</sub> 0- 9-CH <sub>3</sub> - 7-CH <sub>3</sub> 0- 9-CH <sub>3</sub> 0- 9-CH <sub>3</sub> 0- 9-CH <sub>3</sub> 0-	p-f-Ph- p-f-Ph- p-f-Ph- p-f-Ph- p-f-Ph-	333 333 334
7-(1-azetidine) 9-CH3-	m-CH30-Ph-	354		7-(1-pyrrole)	p-F-Ph-	335
7-(1-azetidine) 9-CH1-	m-CH30-Ph-	354		7-(1-pyrrole)	p-F-Ph-	335
8-CH3O-						
6-CH <sub>3</sub> O- 7-CH <sub>3</sub> O- 8-CH <sub>3</sub> O-	п-СИ30-Рh-	353		7-CH <sub>3</sub> O- 9-CH <sub>3</sub> O-	p-F-ph-	334
6-CH <sub>3</sub> O- 7-CH <sub>3</sub> O-	m-CH30-Ph-	353		7-CH30- 9-CH30-	p-F-Ph-	334
<b>,</b>				7-C83- 9-C83-	-6-F-Ph-	333
7- (CH <sub>3</sub> ) 2N- 9-CH <sub>3</sub> S-	m-CH <sub>3</sub> O-Ph-	352		9-CH <sub>3</sub> -	- 40 1 & - L	111
9-CH3S-				7-CH30-	p-F-Ph-	332
7-(N-pyrrolidine)-	m-CH30-Ph-	351		7-CH3S- 9-CH3-	p-F-ph-	331
9-CH3S-						
7-(N)-azetidine 9-CH3S-	m-CH30-Ph-	350		7-9hs- 9-CH <sub>3</sub> -	p-F-Ph-	330
7-(CH <sub>3</sub> ) <sub>2</sub> NH -	m-CH30-Ph-	349		9-CR3-	i	
7-cyclopropyl	m-CH3O-Ph-	348		7-CH <sub>3</sub> S (0) <sub>2</sub> -	p-F-Ph-	
7-CH3C(=CH2)-						329
Ph-	m-CH30-Ph-	347		/-CH3S (0) 9-CH3-	-uz-z-d	329
7-(N)Wmethylpiperazin	m-CH3O-Ph- m-CH3O-Ph-	346		9-CH3- 7-CH3S (0) - 9-CH3-	p-f-Ph-	328
7-(1-pyrazole)	m-CH3O-Ph- m-CH3O-Ph- m-CH3O-Ph-	345		7-EtS 9-CH <sub>3</sub> - 7-CH <sub>3</sub> S (O) - 9-CH <sub>3</sub> -	p-E-Ph-	327 328 329
7- (CH3) 2N- 9-CH3S-	m-CH3O-Ph- m-CH3O-Ph- m-CH3O-Ph- m-CH3O-Ph-	345 345 345 345		7-(1-azetidine) 9-CH <sub>3</sub> - 7-EtS 9-CH <sub>3</sub> - 7-CH <sub>3</sub> S(O)- 9-CH <sub>3</sub> -	p-F-Ph- p-F-Ph- p-F-Ph-	326 323 329 329
7-(N-pyrrolidine) 9-CH3S-	p-F-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph-	343 345 346 346 346 346		6-CK30- 7-CK30- 8-CK30- 7-(1-azetidine) 9-CK3- 9-CK3- 7-CK3S (0)- 9-CK3-	p-F-Ph- p-F-Ph- p-F-Ph-	325 326 327 329
	р-ғ-ғh- р-ғ-ғh- п-сн <sub>3</sub> 0-ғh- п-сн <sub>3</sub> 0-ғh- п-сн <sub>3</sub> 0-ғh-	3 3 3 3 3 3 3 4 3 3 3 4 5 5 5 5 5 5 5 5		7-t-Bu- 6-CK30- 7-CK30- 8-CK30- 7-EK30- 7-ELS- 9-CK3- 7-ELS- 9-CK3-	m-CB30-Ph p-F-Ph- p-F-Ph- p-F-Ph-	325 327 328 329
7-(N)-azetidine 9-CH3S-	р-F-Рh- р-F-Рh- п-СH <sub>3</sub> O-Рh- п-СH <sub>3</sub> O-Рh- п-СH <sub>3</sub> O-Рh- п-СH <sub>3</sub> O-Рh-	341 342 344 344 346 346	· *	7-1Pr- 7-t-Bu- 6-CH3O- 7-CH3O- 8-CH3O- 7-(1-azetidine) 9-CH3- 7-ELS- 9-CH3-	m-CH3O-Ph m-CB3O-Ph p-F-Ph- p-F-Ph- p-F-Ph-	323 324 325 328 328
7-(CH3)2NH 7-(N)-azetidine 9-CH3S-	p-F-Ph- p-F-Ph- p-F-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph-	340 341 342 344 345 345	· · · · · · · · · · · · · · · · · · ·	7-Et- 7-1Pr- 7-t-Bu- 6-CK30- 7-CK30- 8-CK30- 7-(1-azetidine) 9-CK3- 7-EtS- 9-CK3- 7-CK3S(0)- 9-CK3-	m-CH3O-Ph m-CH3O-Ph m-CH3O-Ph p-F-Ph- p-F-Ph-	322 323 324 327 328 329
7-cyclpropyl 7-(CH <sub>3</sub> ) <sub>2</sub> NH 7-(N)-azetidine 9-CH <sub>3</sub> S-	p-F-Ph- p-F-Ph- p-F-Ph- p-F-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph-	339 340 342 344 344 345 346	*	9-CH30- 7-Et- 7-1Pr- 7-LEH30- 8-CH30- 8-CH30- 9-CH3- 9-CH3- 7-CH3S(0)- 9-CH3-	m-CH3O-Ph m-CH3O-Ph m-CB3O-Ph p-F-Ph- p-F-Ph-	323 323 323 324 325 325 325 325 325 325 325 325 325 325
7-CH3C(=CH2)- 7-cyclpropyl 7-(CH3)2NH 7-(N)-azetidine 9-CH3S-	p-F-Ph- p-F-Ph- p-F-Ph- p-F-Ph- p-F-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph- m-CH <sub>3</sub> O-Ph-	338 339 340 342 344 345 345	*	7-CH30- 9-CH30- 7-Et- 7-Et- 7-t-Bu- 6-CH30- 7-CH30- 8-CH30- 7-Et- 9-CH3- 7-CH35(0)- 9-CH3-	m-CH3O-Ph m-CH3O-Ph m-CH3O-Ph m-CH3O-Ph p-F-Ph- p-F-Ph- p-F-Ph-	323 323 323 323 324 325 325 326 329

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374	373	372	371	370	369	368	367	366	365	364	363		362	361		3 60 3 60	359	ш 65	357	6	3 8 6	35 55	
thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl		m-CH <sub>3</sub> O-Ph-	m-CH30-Ph-		m-CK+O-Ph-	m-CH30-Ph-	m-CH3O-Ph-	m-CH3O-Ph-	11 C13 C 6 11		m-CH3O-Ph-	
7-СН30-	7-{1-pyrrole}-	7-t-Bu-	7-1Pr-	7-Et-	7-сн <sub>3</sub> 0- 9-сн <sub>3</sub> 0-	7-CH <sub>3</sub> S- 9-CH <sub>3</sub> S-	7-PhS-	7-CH <sub>3</sub> S (O) 2-	7-CH3S(O)-	7-EtS-	7-(1-aziridine)	9-сн <sub>3</sub> о-	7-сн <sub>3</sub> 0-	7-CH3- 9-CH3-	9-CH3-	7-04-0	7-CH <sub>3</sub> S-	7-phs- 9-CH <sub>3</sub> -	7-CH <sub>3</sub> S (O) 2- 9-CH <sub>3</sub> -	9-CH3-		7-EtS-	
	395	394 4		393	392	بر ش	390	389	388	387	386	385	4	ച പ ഇ വ 4 പ	υ ω ο σο ο Ν	381	380	379	378	377	. 376	375	
	thien-2-yl	tbien-z-yl		thien-2-yl	thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-yl	5-Cl-thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-yl		5-C1-thien-2-y1	5-C1-thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-yl	5-Cl-thien-2-yl	5-C1-thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	
9-CH3-	7-CH <sub>3</sub> S(O) <sub>2</sub> -	/-CH3- 9-CH3-	3 01 010	7-Ets-	7-(l-azetidine) 9-CH <sub>3</sub> -	7-Me	7-CH3S-	7-CH <sub>3</sub> O-	7-t-Bu-	7-1Pr-	7-Et-	· 7-CH30- 9-CH30-	9-CH3S-	7-CH <sub>3</sub> S-	7-CR3S (O) 2-	7-CH3S(O)-	7-EtS-	7-(1-aziridine)	7-(l-azetidine)	7-Me-	7-(1-azetidine)	7-CH3S-	

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7-(N)-azetidine 9-CH <sub>3</sub> S-	7-(N-pyrrolidine)- 9-CH3S-	7 - (CH <sub>3</sub> ) 2N- 9-CH <sub>3</sub> S-		7-(1-aretidine) 9-CH3-	7-EtS- 9-CH3-	7-CH <sub>3</sub> S (0) -	7-CH1S (0) 2-	9-CH3-	7-PhS- 9-CH3-	7-CH3S-	9-CH <sub>3</sub>	9-CR3-	9-043-	7-CH3O- 9-CH3O-	6-CH3O-	8-CH30-	6-CH30-	7-CH30- 8-CH30-			25
5-Cl-thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-yl		5-C1-thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-yl	8-C-1+b4on-2-c]		5-C1-thien-2-yl	5-C1-thien-2-vl		1	5-C1-thien-2-y1	5-C1-thien-2-yl	thien-2-yl		5-C1-thien-2-yl	f			
417	418	419		420	421	422	667	}	424	425		97.	427	428	429		430				
7-Phs- 9-CH <sub>3</sub> -	7-CH <sub>3</sub> S- 9-CH <sub>3</sub> -	7-CH <sub>3</sub> O- 9-CH <sub>3</sub> -	7-CH <sub>3</sub> - 9-CH <sub>3</sub> -	7-снзо- 9-снзо-		7-(1-pyrazrole) 7-(N-N'-methylpiperazine	Ph-	7-CH3C (=CH2)-	7-cyclpropyl	7- (CH3) 2NB -	7-(N)-azetidine 9-CH3S-	7-(N-pyrrolidine) 9-CH3S-	7 - (CH3) 2N-	9-CH35-	7-(1-pyrazrole)	7-(N)-methylpiperazine	-ya	7-CH3C (-CH2)-	7-cyclopropyl	7-(CH <sub>3</sub> ) <sub>2</sub> NH -	365
thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	1	thien-2-y1	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl	thien-2-yl		5-Cl-thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-y1	5-Cl-thien-2-yl	5-C1-thien-2-yl	5-C1-thien-2-y1	
396	397	398	399	400	Ę	402	403	404	405	406	407	408	409		411	412	413	414	415	416	•

### Examples 232-1394 .

positions (R', R', R', R') and in the indicated position structures set forth in Table 1. The starting on the benzo ring (R\*). introduce the indicated substituents in the 4- and 5organic synthesis well known to the art in order to above are varied in accordance with principles of materials illustrated in the reaction schemes shown to the art, compounds are prepared having the necessary other common synthesis expedients well known the substituents to be introduced, including where described in those of Examples 1 to 72 appropriate to Using in each instance a method generally

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#### Example 1395

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Dibutyl 4-fluorobenzene dialdehyde

dialdehyde Step 1: Preparation of dibutyl 4-fluoro benzene

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material was completely consumed, and then 34 g (135 stirred at 75 C for 1.5 hours, or until the starting difluorobenzaldehyde (Aldrich) in 615 mL of DMSO at cooled solution was poured into water and extracted three hours or until the reaction was completed. The mmol) of dibutyl mesylate aldehyde was added at about lithium sulfide (Aldrich). The dark red solution was ambient temperature was added 6.2 g (135 mmol) of To a stirred solution of 17.5 g (123 mmol) of 2,5-The reaction mixture was stirred at 75 C for

30

25

concentrated in vacuo. Silica gel chromatographic with water several times, dried (MgSO,) and with ethyl acetate. The combined extracts were washed

1.5-1.78 (m, 4H), 3.09 (s, 2H), 7.2-7.35 (m, 1H), 7.5-7.6 (m, 2H), 9.43 (s, 1H), 10.50 (d, J = 2.62 Hz, 1H) purification of the crude product gave 23.6 g (59%) of (CDCl<sub>3</sub>) d 0.87 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), fluorobenzene dialdehyde as a yellow oil: 1H NMR

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3.02 Hz, 1H), 7.20 (dd, J = 9.47, 2.82 Hz, 1H), 7.421H), 3.03 (s, 2H), 4.79 (s, 2H), 6.96 (dt, J = 8.46, 6H), 1.0-1.4 (m, 8H), 1.5-1.72 (m, 4H), 1.94 (br s, colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) d 0.88 (t, J = 7.05 Hz. 13.5 g (58%) of recovered starting material, and 8.1 g chromatographic purification of the crude product gave extracted with ethyl acetate, washed with water, dried of DIBAL, followed by 3 N HCl. The mixture was sufficient amount of ethyl acetae to quench the excess 20 hours. To the cooled solution at -40 C was added syringe. The reaction mixture was stirred at -40 C for added 69.8 mL (69.8 mmol) of DIBAL (1M in THF) via a obtained from Step 1 in 650 mL of THF at -60 C was To a solution of 22.6 g (69:8 mmol) of the dialdehyde Step 2: Preparation of dibutyl 4-fluorobenzyl alcoho: (dd, J = 8.67, 5.64, 1H), 9.40 (s, 1H).(36%) of the desired fluorobenzyl alcohol as a (MgSO,), and concentrated in vacuo. Silica gel

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obtained from Step 2 in 100 mL of DMF at -40 C was To a solution of 8.1 g (25 mmol) of benzyl alcohol and ethyl acetate. The extract was washed a few times the mixture was added 10% solution of sodium sulfite cold for 30 min, then was allowed to warm to 0 C. To added 47 g (50 mmol) of bromotriphenyphosphonium Step 3: Preparation of dibutyl 4-fluorobenzyl bromide with water, dried (MgSO4), and concentrated in vacuo. bromide (Aldrich). The resulting solution was stirred

35

acetate/hexane mixture (1:4 ratio) and filtered through

The mixture was stirred in small amount of ethyl

a pad of silica gel, eluting with same solvent mixture.

The combined filtrate was concentrated in vacuo to give

9.5 g (98%) of the desired product as a colorless oil:

<sup>1</sup>H NMR (CDCl<sub>3</sub>) d 0.88 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m,

7.02 (dt, J = 8.46, 3.02 Hz, 1H), 7.15 (dd, J = 9.47, 2.82 Hz, 1H), 7.46 (dd, J = 8.67, 5.64, 1H), 9.45 (s,

8H), 1.55-1.78 (m, 4H), 3.11 (s, 2H), 4.67 (s, 2H),

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Example 1396

from Step 3 in 200 mL of CH,Cl, at 0 0C was added 15.9 g To a solution of 8.5 g (25 mmol) of sulfide obtained

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Preparation of sulfonyl 4-fluorobenzyl

Step 4: bromide

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in yacue to give 10.2 g (98%) of the desired product as a colorless oil:  $^{1}\text{H}$  NMR (CDCl3) d 0.91 (t, J = 7.05 Hz, solution was stirred cold for 10 min, then was allowed with saturated Na,CO,, dried (MgSO,), and concentrated mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed several times to stirred ambient temperature for 5 hours. To the (60 mmol) of mCPBA (64% peracid). The resulting

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6H), 1.03-1.4 (m, 8H), 1.65-1.82 (m, 2H), 1.90-2.05 (m,

7.30 (dd, J = 8.87, 2.42 Hz, 1H), 8.03 (dd, J = 8.86,

5.64, 1H), 9.49 (8, 1H).

2H), 3.54 (s, 2H), 5.01 (s, 2H), 7.04-7.23 (m, 1H),

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Generic Scheme X

sulfide to sulfone yielded the key intermediate w. alcohol to benzyl bromide, followed by oxidation of benzyl alcohol monoaldehyde Z. Conversion of benzyl reduction of the dialdehyde at low temperature yielded provided a dialkyl benzene dialdehyde Y. DIBAL by the addition of dialkyl mesylate aldehyde  $(\mathbf{x})$ , polar solvent (such as DMF, DMA, DMSO ..etc); followed lithium sulfide or other nucleophilic sulfide anion in Generic Scheme X: The nucleophilic substitution of an appropriately substituted 2-fluorobenzaldehyde with

## Preparation of N-propylsulfonic acid

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8.12-8.25 (m, 1H); MS ES- M-H m/z 579. 1H), 6.45-6.58 (m, 1H), 6.92-7.02 (m, 1H), 7.35-7.41 of m, 5H), 3.58-3.76 (m, 2H), 4.15 (s, 1H), 5.51 (s, using acetonitrile/water as eluent (30-45%) and  $\mu$ m). The reaction was stirred in a sealed vial at 55 To a solution of 51 mg (111 µm) Compound X in ethanol 1.11-1.52 (m of m, 10H), 1.58-1.72 (m, 1H), 2.08-2.21 afforded the desired material as an off-white solid (m, 1H), 7.41-7.51 (m, 2H), 8.08 (d, J = 8.1 Hz, 1H)(28.4 mg, 44%): 'H NMR (CDCL) d 0.82-0.96 (m, 6H), stream and purified by reversed phase chromatography °C for 25 hr. Sample was concentrated under a nitrogen (400 μl) was added 1,3 propane sultone (19.5 μl, 222 (m, 1H), 2.36-2.50 (m, 2H), 2.93 (s, 6H), 3.02-3.22 (m

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analogs. The following example demonstrates the reacted with sulfur and nitrogen nucleophiles to give the corresponding sulfur and nitrogen substituted benzothiepine compounds of this invention can be The 7-fluoro, 9-fluoro and 7,9-difluoro analogs of

synthesis of these analogs.

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methylthio-2, 3, 4, 5-tetrahydrobenzothiepine-1, 1-dioxide. 3,3-Dibuty1-5a-(4'-fluorophenyl)-4a-bydroxy-7-

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A mixture of 0.4 g Of 3,3-dibutyl-7-fluoro-5a-(4'fluorophenyl \-4a-hydroxy-2,3,4,5-

ether extract was dried over  ${\rm MgSO}_4$  and concentrated in EtOAc in hexane) gave 0.26 g of needles, mp 164-165.5 methanethiolate was added to the reaction mixture and vacuo to 0.44 g of an oil. Purification by HPLC (10% methanethiolate and 20 ml of DMF was stirred at 50 C the mixture was stirred for additional 20 h at 50 C triturated with water and extracte wilth ether. The tetrahydrobenzothiepine-1,1-dioxide, prepared by then was concentrated in vacuo. The residue was previously described method, 0.12 g of sodium for 3 days. An additional 0.1 g of sodium

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Bis (dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-3,3-Dibutyl-9-dimathylamino-7-fluoro-5a-(4'tetrahydrobenzothiepine-1,1-dioxide and 7,9fluorophenyl)-4a-hydroxy-2,3,4,5-

hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.

tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 480 and concentrated in vacuo. The residue was triturated dimethylamine in THF was heated at 160 C in a sealed 5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-(M<sup>+</sup> +1). tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 505 (4'-fluorophenyl)-4a-hydroxy-2,3,4,5identified as 7,9-bis(dimethylamino)-3,3-dibuty1-5a- $(M^+ +1)$ , and 29 mg of a later fraction which was The resdue was purified by HPLC (10% EtOAc in hexane) extract was dried over  ${
m MgSO_d}$  and concentrated in vacuo. with 25 ml of water and extracted with ether. The ether Parr reactor overnight. The reaction mixture was cooled method described previously, in 20 ml of 2 N tetrahydrobenzothiepine-1,1-dioxide, prepared by the (4'-fluorophenyl)-4a-hydroxy-2,3,4,5identified as 3,3-dibutyl-9-dimethylamino-7-fluoro-5ato give 35 mg of an earlier fraction which was A solution of 0.105 g of 3,3-dibutyl-7,9-difluoro-

sulfate as the reagent. example describes a procedure for using the cyclic reagent as shown in the following scheme. The following synthesized using cyclic sulfate (A, below) as the The compounds of this invention can also be

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$$(R^{n})_{q}$$
 $(R^{n})_{p}$ 
 $$(R^{n})_{q}$$

$$(R^{n})_{p}$$

$$(R^{n})_{q}$$

$$(R^{n})_{p}$$

$$(R^{n})_{q}$$

$$(R^{n})_{p}$$

$$(R^{n})_{p}$$

$$(R^{n})_{p}$$

Str

Dibutyl cyclic sulfite:

left. The mixture was washed with ice water twice then magnesium sulfate and concentrated under vacuum to give stirred at 0 degrees C under nitrogen. To the mixture, thionyl chloride (97.8 g, 0.82 mol) was added dropwise (103g, 0.548 mol) and triethylamine (221g, 2.19 mol) half an hour. The reaction mixture was stirred for 3 the cyclic sulfite 128 g (100%) as a black oil. Mass and within 5 min the solution turned yellow and then turned black when the addition was completed within with brine twice. The organic phase was dried over A solution of 2,2-dibutyl-1,3-propandiol hrs. GC showed that there was no starting material in anhydrous methylene chloride (500 ml) and was spectrum (MS) was consistent with the product.

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To a solution of the above compound (127.5g , 0.54 starting material left. The mixture was extracted with cyclic sulfate 133 g (97.8%) as an oil. Proton, carbon mol) in 600 ml acetonitrile and 500 ml of water cooled the solution turned black. GC showed that there was no 300 ml of ether and the ether extract was washed three in an ice bath under nitrogen was added ruthenium(III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of filtrate was concentrated under vacuum and gave the times with brine. The organic phase was dried over magnesium sulfate and passed through celite. The NMR and MS were consistent with the product.

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methylphenylthio)methyl]-2-butylhexanol: 2-[(2-(4'-Fluorobenzyl)-4-

successively with water and brine, dried over magnesium boiled for 30 min and cooled, acidified with 6N HCl and boiled for 10 min. The reaction mixture was cooled and 10 ml of 2-methoxyethyl ether was added dropwise to the sulfate and concentrated under vacuum to give 2.47 g ( GC showed that there was no thiol left. The Sodium hydride (60% oil dispersion), 0.27 g (6.68 mmole), was washed with hexane and the hexane wash was decanted. To the washed sodium hydride was added 20 ml mmole) of 2-(4'-fluorobenzyl)-4-methylbenzenethiol in reaction mixture in 15 min. A mixture of 2.17 g (8.68 of 2-methoxyethyl ether (diglyme) and the mixture was methoxyethyl ether was added once and stirred for 30 solvent was evaporated and triturated wth water then was extracted with ether twice. The water layer was separated, treated with 20 ml of 10% NaOH then was extracted with ether. The organic layer was washed mmole) of the dibutyl cyclic sulfate in 10 ml of 2-92.5%) of an oil. Proton NMR ,  $^{13}\mathrm{C}$  NMR and MS were min at 0 C then at room temperature for 1 hr under cooled in an ice bath. A solution of 1.55 g (6.68 consistent with the product.

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2-[(2-(d'.-Fluorobonzyl)-dmethylphenylthio)methyl]-2-butylhexanol;

To a solution of the above product (2 g , 4.9 mmol) in 40 ml methylene chloride cooled in an ice bath under nitrogen was added pyridinium chlorochromate (2.18 g, 9.9 mmol) at once. The reaction was stirred with 3 hrs and filtered through a bed of silica gel. The filtrate was concentrated under vacuum to give 1.39 g (70%) of an oil. Proton, carbon NMR and MS were consistent with the product.

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2-[(2-(d'-Fluorobonmyl)-d-mothylphonyloulfonyl)methyl]-2-butylhoxanal

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To a solution of the above product (0.44 g ,1.1 mmole) in 20 ml methylene chloride solution cooled in an ice bath under nitrogen was added 70% mchloroperbenzoic acid (0.54 g, 2.2 mmol) at once. The reaction mixture was stirred for 18 hrs and filtered. The filtrate was washed successively with 10% NaOH (3X), water and brine, dried over magnesium sulfate and concentrated under vacum to give 0.42 g (90%) of an oil. Proton, carbon NMR and MS were consistent with the product.

3,3-Dibutyl-7-methyl-5a-(4'-fluorophenyl)-4abydroxy-2,3,6,5-tetrahydrobenzothlopino-1,1-dioxido: 5

A mixture of 0.37 g (0.85 mmol) of the above product in 30 ml of anhydrous THP was stirred at 0 %C. Then potassium t-butoxide (102 mg, 0.85 mmol) was added. After 3 hrs, TLC showed that there was a product and some starting material left. The crude reaction mixture was acidified with 10% HCl and extracted with ether. The ether extract was washed successively with water and brine, dried with MgSO $_4$  and concentrated under vacuum. The residue was purified by HPLC (10% EtOAc-Hexane). The first fraction was 0.1 g of starting material as an oil and the second fraction was a white solid, 0.27 g (75%). Proton NMR and carbon NMR were consistent with the desired product. Mass spectrum (CI)

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also confirmed the product, m/e 433 ( $M^+$  1).

Step 1

C, H, CINO, fw=291.69

via syringe and begin stirring with magnetic stir bar. anhydrous chlorobenzene (Aldrich 28,451-3) to the PC1, phosphorus pentachloride (0.328mole Aldrich 15,777-5) into a 2-necked 500ml round bottom flask. Fit flask with a N, inlet adapter and suba seal. Remove from In an inert atmosphere, weigh out 68.3 gms inert atmosphere and begin N, purge. Add 50mls

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Wash temperature for ~20hrs, place in oil bath and heat at chlorobenzene solution while under N, purge. Stir at room temperature overnight. After stirring at room Weigh out 60 gms 2-chloro-5-nitrobenzoic acid 50C for 1hr. Remove chlorobenzene by high vacuum. (0.298 mole Aldrich 12,511-3). Slowly add to the residue with anhydrous hexane. Dry acid chloride wt=61.95gms. Store in inert and dry atmosphere.

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105mls anhydrous anisole (0.97 mole Aldrich 29,629-5). Place solution in a 2-necked 500ml round bottom flask. In inert atmosphere, dissolve acid chloride with

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adapter. Remove from inert atmosphere. Chill reaction Fit reaction flask with addition funnel and a N, inlet Aldrich 29,471-3) and place in a solid addition funnel. solution with ice bath and begin N, purge. Slowly add Weigh out 45.1gms aluminum chloride (0.34 moles

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AlC1, to chilled solution. After addition is complete, allow to warm to room temperature. Stir overnight .

acetate. Dry on vacuum line. Wt=35.2gms. Yield 41% filter and rotovap to dryness. Remove anisole by high vacuum. 2% NAOH, then twice with deionized H,O. Dry with MgSO, ether. Combine organic layers and extract twice with mls 1N HCl and ice. Stir 15 min. Extract twice with Obtain NMR and mass spec (m/z=292). Quench reaction by pouring into a solution of 300 Crystalize product from 90% ethanol 10% ethyl

Step 2

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C,H,ClNO, fw=277.71

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stir bar. Chill solution with ice bath. chloride. Place in a 3 liter flask fitted with  $N_1$ inlet, addition funnel and stopper. Stir with magnetic benzophenone from step 1 in 250mls anhydrous methylene Dissolve 38.10gms (0.131 moles) of the

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Stir 5 minutes after addition is complete. sulfonic acid (0.262 mole Aldrich 15,853-4) and 170 funnel and add dropwise to chilled solution under  $N_{
m r}$ . mls anhydrous methylene chloride. Prepare a solution of 39.32 gms trifluoromethane Place in addition

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methylene chloride. Place in addition funnel and add after addition is complete. dropwise to chilled solution under N, Stir 5 minutes (0.197mole Aldrich 23,019-7) and 170mls anhydrous Prepare a solution of 22.85 gms triethyl silane

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C,H,,NO,S fw=443.61

trifluoromethane sulfonic acid and 170mls anhydrous Prepare a second solution of 39.32 gms 30

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dropwise to chilled solution under N<sub>2</sub>. Stir 5 minutes methylene chloride. Place in addition funnel and add after addition is complete.

silane and 170mls anhydrous methylene chloride. Place overnight. warm to room temperature overnight. Stir under N, under N,. After all additions are made allow to slowly in addition funnel and add dropwise to chilled solution Prepare a second solution of 22.85 gms triethyl

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extract aqueous layer 2 times with methylene chloride. chilled temperature for 30 min. Pour into a separatory vigorously, slowly add reaction mixture. Stir at beaker. Chill with ice bath. While stirring by NMR and mass spec (m/z=278). ethanol. Dry on vacuum line. Dry wt=28.8gms. Confirm funnel and allow separation. Remove organic layer and Dry organic layers with MgSO, Crystallize from Prepare 1300 mls saturated NaHCO, in a 4 liter

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Step 3

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bath and heat at 75°C under N, overnight then cool to condenser, N, inlet, and stopper. Add 1.84 gms Li,S flask with magnetic stir bar. Fit flask with water 200 mls anhydrous DMSO. Place in a 500 ml round bottom (0.040 moles Aldrich 21,324-1). Place flask in oil Dissolve 10.12 gms (0.036 moles) of product 2 with

room temperature.

reaction solution. Purge well with N,, heat overnight Weigh out 10.59 gms dibutyl mesylate (0.040 moles). Dissolve with anhydrous DMSO and add to at 80°C.

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4gSO,, filter and rotovap to dryness. Dry oil on vacuum with ether 3 times. Combine organic layers and extract Cool to room temperature. Prepare 500 mls of 5% slowly add reaction mixture. Stir 30 min. Extract. using 95% hexane and 5% ethyl acetate as the mobile Obtain pure product by column chromatography with water and sat'd NaCl. Dry organic layer with acetic acid in a 2 liter beaker. While stirring, phase. Dry wt=7.8 gms. Obtain NMR and mass spec m/z=444).

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Step 4

C,H,,NO,S fw=475.61

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temperature and monitor reaction by TLC. Reaction goes Dissolve 9.33 gms (0.021 moles) of product 3 with 120 mls anhydrous methylene chloride. Place in a 250 flask with N, inlet and stopper. Chill solution with ml round bottom flask with magnetic stir bar. Fit chloroperbenzoic acid (0.0435 moles, Fluka 25800, ice bath under N, purge. Slowly add 11.54 gms 3--65%). After addition is complete warm to room

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pure product by crystallizing from ethanol or isolating with methylene choride. Combine organic layers and dry quickly to the sulphoxide intermediate but takes 8 hrs to convert to the sulphone. Chill solution over night filtrate with 10% K,CO,. Extract aqueous layer twice by column chromatography. Obtain NMR and mass spec with MgSO, Filter and rotovap to dryness. Obtain in freezer. Filter solid from reaction, extract (m/z=476).

'n

Step 5

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C,,H,,NO,S fw=473.68

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stirred mini reactor. Place 9.68 gms (0.0204 moles) of rate of 250 rpm. Run overnight under these conditions. under H,. Run reaction at 200 psig H, 55°C, and a stir product 4 in reactor base. Add 160 mls ethanol. For formaldehyde (0.204 moles, Aldrich 25,254-9, about 37 Reaction is done in a 300 ml stainless steel Parr bag. Purge reactor three times with H,. Heat to 55°C 20,569-9). Seal reactor before removing from glove safety reasons next two compounds are added in a N, atmosphere glove bag. In glove bag, add 15.3 mls at% in water) and 1.45 gms 10% Pd/Carbon (Aldrich

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Cool reactor and vent H,. Purge with N,. Check desired product and intermediate. Filter reaction progress of run by TLC. Reaction is a mixture of

Rotovap and redissolve with ether. Extract with water. mixture over a bed of celite washing well with ether. dryness. Dry on vacuum line. Dry organic layer with MgSO,, filter and rotovap to

line. ether and extract with water. Dry organic layer with well with ether. Rotovap to dryness. Dissolve with Purge with N,. Filter over a bed of celite, washing to the desired product. Cool and vent H, pressure. After second run all of the material has been converted reactor and run overnight under same conditions. MgSO,, filter and rotovap to dryness. Dry on vacuum Charge reactor again with same amounts, seal Obtain NMR and mass spec (m/z=474).

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Step 6

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C,,H,,NO,S fw=473.68

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complete, continue to stir at -10°C monitoring by TLC  $N_{\!\scriptscriptstyle 2}$  purge. Slowly add 2.55 gms potassium t-butoxide and stopper. Chill solution with ice/salt bath under 135 mls anhydrous THF. Place in a 250 ml round bottom 10% HCl stirring 10 min. Extract three times with (0.227 mole Aldrich 15,667-1). After addition is flask with magnetic stir bar. Fit flask with N, inlet Once reaction is complete, quench by adding 135 mls Dissolve 8.97 gms (0.0189 mole) of product 5 with

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NMR and mass spec (m/z=474). rotovap to dryness. Crystallize from ether. Obtain ether. Dry organic. layer with MgSO, filter and

Step 7

C,H,NO,S fw=459.65

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100 mls anhydrous chloroform. Place in a 250 ml round syringe, 2.84 mls boron tribromide (0.03 moles Aldrich bottom flask with magnetic stir bar. Fit flask with N complete in 3 hrs. Monitor reaction progress by TLC. Reaction is usually addition then allow to warm to room temperature. 20,220-7). Stir at cold temperature for 15 min after ice /acetone bath under a N, purge. Slowly add, via inlet adapter and suba seal. Chill solution with dry Dissolve 4.67 gms (0.01 moles) of product 6 with

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10% K,CO, while stirring rapidly. Stir 10 min. then and mass spec (m/z=460). dryness. Crystallize product from ether. Dry organic layer with MgSO, filter and rotovap to HCl, once H,O, and once with saturated NaCl solution aqueous layer. Extract organic layer once with 10% transfer to sep funnel and allow separation. Remove Chill solution with ice bath. Quench with 100 mls Obtain NMR

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Step 8

C,1H,NO,SI fw=701.71

Weigh 0.38 gms NaH (9.57 mmoles Aldrich 19,923-0 flask with magnetic stir bar. Fit flask with N, inlet 60% disp. in mineral oil) in a 250 ml round bottom and stopper. Chill NaH with ice bath and begin N,

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Dissolve 4.0 gms (8.7 mmoles) of product 7 with 60 temperature for 30 min. Add 1.33 gms K,CO, (9.57 mmoles mls anhydrous DMF. Add to the cold NaH. Stir at cold Fisher P-208).

(43.5 mmoles Aldrich 33,343-3) with 60 mls anhydrous Dissolve 16.1 gms 1,2-bis-(2-iodoethoxy)ethane DMF. Add to cold reaction mixture. Warm to room temperature then heat to 40°C overnight under N,.

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pure product by column chromatography using 75% hexane 25% ethyl acetate as the mobile phase. Obtain NMR and Dry organic layer with MgSO, filter and dry. Obtain sequentially with 5% NaOH, H,O, and saturated NaCl. Cleanup by diluting with ether and extracting nass spec (m/z=702).

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Step 9

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C,,H,,N,O,SI fw=802.90

Dissolve 1.0 gms (1.43 mmoles) of product 8 with Fischer-Porter pressure reaction vessel with magnetic acetonitrile. Purge well with N, then close system . Heat at 45°C. Monitor reaction by TLC. Reaction is 10 mls anhydrous acetonitrile. Place in a 3 ounce stir bar. Add 2.9 gms triethyl amine (28.6 mmoles Aldrich 23,962-3) dissolved in 10 mls anhydrous usually complete in 48 hrs.

Perform cleanup by removing acetonitrile under vacuum. Redissolve with anhydrous chloroform and Repeat several times. Dry to obtain crystalline precipitate quaternary ammonium salt with ether. product. Obtain NMR and mass spec (m/z=675).

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Step 1. Preparation of 1

J = 7.45, 1H), 7.50 (s, 1H). 3.39 (s, 3H), 4.42 (s, 2H), 7.18-7.27 (m, 2H), 7.12 (d, (80%) of 1 as a clear colorless liquid. 'H NMR (CDCl,) d plug using hexanes (100%) as elutant yielded 103.2 g Purified by silica-gel chromatography through a 200 mL extracted three times with ethyl acetate. The organic Poured reaction contents into 1.0 L of water and Stirred at ambient temperature for fifteen minutes. of methyliodide (80 mL, 1282 mmol) via addition funnel. mmol) slowly via addition funnel. Then was added 182 g DMSO was added 120 g of 2-bromobenzyl alcohol (641 layer was dried over MgSO, and concentrated in vacuo. To a solution of 144 g of KOH (2560 mmol) in 1.1 L of

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#### Step 2. Preparation of 2

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mixture was stirred at ambient temperature for 18 °C and to it was added 6 g of Pd(PPh,), (5.2 mmol) and thirty minutes, allowed to warm to 5 C, cooled to ~10 dissolved in 500 ml THF. The mixture was stirred then to it was added 180 g of zinc iodide (566 mmol) in 1.5 L THF was added 240 mL of 2.5 M n-butyl lithium To a cooled (-78 °C) solution of 95 g (472 mmol) of 1 125 g 2,5-difluorobenzoyl chloride (708 mmol). The (576 mmol). The mixture was stirred for one hour, and

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NMR (CDC1) d 3.40 (s, 3H), 4.51 (s, 2H), 7.12-7.26 (m, elutant gave 53.6 g (43 %) of 2 as an orange oil. 'H 7.73 (d, J = 7.45, 1H), 7.80 (s, 1H). 3H), 7.47 (t, J = 7.50, 1H), 7.57 (d, J = 7.45, 1H), <u>ναςυο</u>. Purification by silica gel chromatography organic layer was dried over MgSO, and concentrated in organic layer with 1N HCL and with 1N NaOH. The partitioned between ethyl acetate and water, and washed hoursand then cooled to 10 °C, quenched with water, (Waters Prep-500) using 5% ethyl acetate/hexanes as

### Step 3. Preparation of 3

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of 3 as a yellow oil. H NMR (CDCl,) d 0.86 (t, J = 7.25silica gel chromatography (Waters Prep-500) using 10% extracted with methylene chloride, dried organic layer and 2.82 Hz, 1H), 7.16 (dt, J = 8.19 Hz and 2.82 Hz, Hz, 6H), 1.10 - 1.26 (m, 12H), 2.83 (s, 2H), 3.32 (s, ethyl acetate / hexanes as elutant gave 42.9 g (48 %) over MgSO, and condensed in vacuo. Purification by refluxed 2 days. Cooled to ambient temperature and with diethyl ether. Aqueous layer acidified (pH 1) and Added 1 L water to organic residue and extracted twice mmol) in 50 mL DMF was added. Stirred at ambient 1H), 7.45 (t, J = 7.65 Hz, 1H), 7.56-7.61 (m, 2H), 7.69 2H), 3.40 (s, 3H), 4.48 (s, 3H), 7.02 (dd, J = 8.26 HzA solution of 53 g (202.3 mmol) of 2 and 11.2 g Li2S (d, J = 7.85 Hz, 1H), 7.74 (s, 1H).temperature for 18 hours then condensed in vacuo (the cyclic sulfate compound of example 1397) (242.8 hours. The reaction was cooled (0  $^{\circ}$ C) and 60.7 g of X' (242.8 mmol) in 250 mL DMF was heated to 100 °C for 18

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Droparation of A

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elutant gave 24.2 g (60%) of 4 as a oil. 'H NMR (CDC1,) d (30.7 mL, 192.4 mmol). Stirred at -20 °C for two hours, (t, J = 5.84 Hz, 1H), 2.81 (s, 2H), 3.38 (s, 3H), 3.43 (d, J = 5.23 Hz, 2H), 4.16 (s, 2H), 4.42 (s, 2H), 6.80 quenched with water and warmed to ambient temperature. (d, J = 7.45 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.25 - 7.32To a cooled (-40 °C) solution of 42.9 g (96.2 mmol) of (Waters Prep-500) using 10% ethyl acetate/ hexanes as 0.89 (t, J = 7.05 Hz, 6H), 1.17 - 1.40 (m, 12H), 1.46 (d, J = 9.67 Hz, 1H), 6.90 (t, J = 8.46 Hz, 1H), 7.09 3 in 200 mL of methylene chloride was added 21.6 g dried the organic layer over MgSO, and condensed in followed by the addition of 22.4 g triethyl silane trifluoromethane sulfonic acid (12.8 mL, 144 mmol) Partitioned between methylene chloride and water, Vacuo. Purification by silica gel chromatography (m, 2H), 7.42 (m, 1H)

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Step 5. Preparation of 5

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To a cooled (15-18 °C) solution of 24.2 g (55.8 mmol) of 4 in 100 mL DMSO was added 31.2 g sulfur trioxide pyridine complex (195 mmol). Stirred at ambient temperature for thirty minutes. Poured into cold water

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and extracted three times with ethyl acetate. Washed organics with 5% HCl (300 mL) and then with brine (300 mL), dired organics over MgSO, and condensed in vacuo to give 23.1 g (96 %) of 5 as a light brown oil. "H NNTR (CDCl.) d 0.87 (t, J = 7.05 Hz, 6H), 1.01 - 1.32 (m, 8H), 1.53 - 1.65 (m, 4H), 2.98 (s, 2H), 3.38 (s, 3H), 4.15 (s, 2H), 4.43 (s, 2H), 6.81 (dd, J = 9.66 Hz and 2.82 Hz, 1H), 6.91 (t, J = 8.62 Hz, 1H), 7.07 (d, J = 7.46 Hz, 1H), 7.14 (s, 1H), 7.19 (d, J = 7.65 Hz, 1H), 7.26 - 7.32 (m, 1H), 7.42 (dd, J = 8.66 Hz and 5.64 Hz, 1H), 9.40 (s, 1H).

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Step 6. Preparation of 6

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To a cooled (0 °C) solution of 23.1 g (53.6 mmol) of 5 in 200 mL methylene chloride was added 28.6 g meta cholorperoxy-benzoic acid (112.6 mmol). Stirred at ambient temperature for 24 hours. Quenched with 100 mL 10% Na,SO,, partitioned between water and methylene chloride. Dried organic layer over MgSO, and condensed in vacuo to give 24.5 g (98%) of 6 as a light yellow oil. 'H NMTR (CDC1,) d 0.86 - 1.29 (m, 14H), 1.58 - 1.63 (m, 2H), 1.82 - 1.91 (m, 2H), 3.13 (s, 2H), 3.39 (s, 3H), 4.44 (s, 2H), 4.50 (s, 2H), 6.93 (d, J = 9.07 Hz, 1H), 7.10 - 7.33 (m, 5H), 8.05 (s, 1H), 9.38 (s, 1H).

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Step 7. Preparartion of 7

2.61 Hz, 1H), 7.13 (d, J = 7.45 Hz, 1H), 7.21 (s, 1H), 4.44 (s, 2H), 6.42 (s, 1H), 6.58 (dd, J = 9.0 Hz and1.80 (m, 2H), 2.98 (s, 8H), 3.37 (s, 3H), 4.41 (s, 2H), 6H), 0.93 - 1.29 (m, 8H), 1.49 - 1.59 (m, 2H), 1.70 colorless oil. H NMR (CDCl<sub>2</sub>) d 0.85 (t,  $J \approx 7.25 \text{ Hz}$ , acetate/hexanes gave 21.8 g (84 %) of 7 as a clear chromatography (Waters Prep-500) using 15 % ethyl was cooled to ambient temperature and the contents and heated to 110 °C for 16 hours. The reaction vessel 20 mL of neat dimethyl amine. The vessel was sealed concentrated in <u>yacuo</u>. Purification by silica gel added 100 mL of a 2.0 M solution of dimethyl amine and THP contained in a stainless steel reaction vessel was To a solution of 24.5 g (52.9 mmol) of 6 in 20 mL of (t, J = 7.85 Hz, 1H), 7.82 (d, J = 9.06 Hz, 1H),

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Step 8. Preparation of 8

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was cooled to 0 °C. 58.2 mL of a 1 M solution of potassium A solution of 21.8 g (44.8 mmol) of 7 in 600 mL of THF

t-butoxide was added slowly, maintaining the temperature at <5 °C. Stirred for 30 minutes, then

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the elutant to give 3.0 g of 8 as a white solid. mother liquor was purified by silica gel chromatography and water, dried over MgSO4 and concentrated in vacuo. acetate/hexanes gave 15.1 g of 8 as a white solid. The Purification by recrystalization from ~10% ethyl The organic layer was partitioned between ethyl acetate quenched with 50 mL.of saturated ammonium chloride (FABLi') m/e 494.6. HRMS (EI') calculated for M+H (Waters Prep-500) using 30% ethyl acetate/hexanes as Found 487.2746.

### Step 9. Preparation of 9

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chloride and water, dried over MgSO, and concentrated IM solution of boron tribromide was added. Stirred at methylene chloride was cooled to -60 °C. 4.1 mL of a calculated for M 536.1834. Found 536.1822. as a white solid. ethyl acetate/methylene chloride gave 1.95 g (89%) of 9 The organic layer was partitioned between methylene reaction to ~10 °C and quenched with 50 mL of water. ambient temperature for thirty minutes. Cooled A solution of 2.0 g (4.1 mmol) of 8 in 20 mL of in yacuo. Purification by recrystalization from 50% MS (FABH') m/e 537. HRMS (FAB)

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Step 10. Preparation of 10

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A solution of 1.09 g (2.0 mmol) of 9 and 4.9 g (62 mmol) of pyridine in 30 mL of acetonitrile was stirred at ambient temperature for 18 hours. The reaction was concentrated in vacyg. Purification by recrystallization from methanol/ diethyl ether gave 1.19 g (96%) of 10 as an off white solid. MS [FAB') m/e 535.5.

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Example 1398

Step 1. Preparation of 2

To a solution of 6.0 g of dibutyl 4-fluorobenzene dialdehyde of Example 1395 (14.3 mmol) in 72 mL of toluene and 54 mL of ethanol was added 4.7 g 3-nitrobenzeneboronic acid (28.6 mmol), 0.8 g of tetrakis (triphenylphosphine) palladium(0) (0.7 mmol) and 45 mL of a 2 M solution of sodium carbonate in water. This heterogeneous mixture was refluxed for three hours, then cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over MgSO, and concentrated in yacuo.

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Purification by silica gel chromatography (Waters Prep-2000) using ethyl acetate/hexanes (25/75) gave 4.8 g (73%) of the title compound as a yellow solid. 'H NMR (CDCl,) d 0.88 (t, J = 7.45 Hz, 6H), 0.99-1.38 (m, 8H), 1.62-1.75 (m, 2H), 1.85-2.00 (m, 2H), 3.20 (s, 2H), 4.59 (s, 2H), 6.93 (dd, J = 10.5 and 2.4 Hz, 1H), 7.15 (dt, J = 8.4 and 2.85 Hz, 1H), 7.46-7.59 (m, 2H), 8.05-8.16 (m, 3H), 9.40 (s, 1H).

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Step 3. Preparation of 3

9.9 and 3.6 Hz, 1H), 8.23-8.30 (m, 1H), 8.44 (s, 1H). 6.0 Hz, 1H), 5.67 (s, 1H), 6.34 (dd, J=9.6 and 3.0 Hz,  $MS(FABH^+)$  m/e (relative intensity) 464.5 (100), 446.6 8.1 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.13 (dd, J =1H), 7.08 (dt, J = 8.5 and 2.9 Hz, 1H), 7.64 (t, J =eluent yielded 4.3 g (90%) of 3 as a pale yellow foam chromatography through a 100 ml plug using CH,Cl, as and concentrated in vacuo. Purification by silica gel organic layer was washed with brine, then dried (MgSO,) of saturated ammonium chloride. The mixture was the temperature at <5 °C. Stirring was continued for of potassium t-butoxide was added slowly, maintaining (65). HRMS calculated for M+H 464.1907. Found H NMR (CDCl<sub>1</sub>) d 0.93 (t, J = 7.25 Hz, 6H), 1.00-1.55 partitioned between ethyl acetate and water; the 30 minutes, then the reaction was quenched with 100 mL cooled to 0 °C in an ice bath. 20 mL of a 1 M solution A solution of 4.8 g (10.4 mmol) of 2 in 500 mL THF was  $(q_{AB}, J_{AB} = 15.0 \text{ Hz}, \Delta V = 33.2 \text{ Hz}, 2H), 4.17 (d, J = 1.00)$ (m, 8H), 1.59-1.74 (m, 3H), 2.15-2.95 (m, 1H), 3.16

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Step 4. Preparation of 4

 $MS(FABH^+)$  m/e (relative intensity) 489.6 (100), 471.5 1H), 8.20 (dd, J = 8.4 and 1.2 Hz, 1H), 8.43 (s, 1H). 6.52 (dd, J = 9.6 and 2.7 Hz, 1H), 7.59 (t, J = 8.4 Hz) 1H), 7.85 (d, J = 7.80 Hz, 1H), 7.89 (d, J = 9.0 Hz, = 9.0 Hz, 1H), 5.65 (s, 1H), 5.75 (d, J = 2.1 Hz, 1H),1.60-1.69 (m, 3H), 2.11-2.28 (m, 1H), 2.79 (s, 6H), acetate) gave 4.0 g (88%) of 4 as a yellow solid. 'H and the contents concentrated in yacuo. Purification vessel was sealed and heated to 110 °C for 16 hours. vessel was added 8.2 g dimethyl amine (182 mmol). The 3 in 30 ml THF contained in a stainless steel reaction 489.2456.  $3.09 (q_{AB}, J_{AB} = 15.0 \text{ Hz}, DV= 45.6 \text{ Hz}, 2H), 4.90 (d, J)$ NMR (CDCl<sub>3</sub>) d 0.80-0.95 (m, 6H), 0.96-1.53 (m, 8H), an ethyl acetate/hexanes gradient (10-40% ethyl by silica gel chromatography (Waters Prep-2000) using The reaction vessel was cooled to ambient temperature (25). HRMS calculated for M+H 489.2423. Found To a cooled (0 °C) solution of 4.3 g (9.3 mmol) of

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Step 5. Preparation of 5

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ethanol in a stainless steel Parr reactor was added 1 g contents filtered to remove the catalyst. The filtrate sealed, purged twice with H,, then charged with H, (100 IH), 6.52 (dd, J = 12.2 and 2.6 Hz, 1H), 6.65 (dd, J =4z, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.9 Hz, was concentrated in vacuo to give 0.9 g (96%) of 5. 'H psi) and heated to 45 °C for six hours. The reaction 1H). MS(PABH<sup>+</sup>) m/e (relative intensity) 459.7 (100). 1.07 ( $q_{AB}$ ,  $J_{AB} = 15.1$  Hz, DV = 44.2 Hz, 2H), 3.70 (s, 2H), 4.14 (s, 1H), 5.43 (s, 1H), 6.09 (d, J = 2.4 Hz, 7.8 and 1.8 Hz, 1H), 6.83 (s, 1H), 6.93 (d, J = 7.50NMR (CDC1,) d 0.80-0.98 (m, 6H), 1.00-1.52 (m, 10H), ..52-1.69 (m, 1H), 2.15-2.29 (m, 1H), 2.83 (s, 6H), To a suspension of 1.0 g (2.1 mmol) of 4 in 100 ml HRMS calculated for M+H 459.2681. Found 459.2670. 10% palladium on carbon. The reaction vessel was ressel was cooled to ambient temperature and the

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Step 6. Preparation of 6

7.32-7.41 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.90 (d, J4H), 2.38 (t, J = 6.9 Hz, 2H), 2.80 (s, 6H), 3.07 ( $q_{AB}$ , using a gradient of ethyl acetate(20-50%) in hexane as H NWR (CDC1,) d 0.84-0.95 (m, 6H), 1.02-1.53 (m, 10H), JAB = 15.6 Hz, DV = 40.4 Hz, 2H), 3.43 (t, J = 6.9 Hz, eluent yielded 0.9 g (73%) of 6 as a pale yellow oil. was added 800 mg (4.0 mmol) 5-bromovaleroyl chloride. Next was added 4 g (39.6 mmol) TEA. The reaction was silica gel chromatography through a 70 ml MPLC column IH), 6.51 (dd, J = 9.3 and 2.7 Hz, 1H), 7.28 (s, 1H), 2H), 4.10 (s, 1H), 5.51 (s, 1H), 5.95 (d, J = 2.4 Hz, To a solution of 914 mg (2.0 mmol) of 5 in 50 ml THF 1.53-1.68 (m, 1H), 1.80-2.00 (m, 4H), 2.12-2.26 (m, (MgSO,) and concentrated in vacuo. Purification by stirred 10 minutes, then partitioned between ethyl The organic layer was dried acetate and brine. = 9.0 Hz, 1H).

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Step 7. Preparation of 7

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Purification by reverse-phase silica gel chromatography (Waters Delta Prep 3000) using an acetonitrile /water To a solution of 0.9 g (1.45 mmol) of 6 in 25 ml acetonitrile add 18 g (178 mmol) TEA. Heat at 55 °C or 16 hours. The reaction mixture was cooled to ambient temperature and concentrated in vacug.

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1H), 9.22 (s, 1H). HRMS calcd 642.4304; observed J = 8.4 Hz, 1H, 7.74 (s, 1H), 7.88 (d, J = 9.0 Hz,1.8 Hz, 1H), 6.57 (dd, J = 9.3 and 2.7 Hz, 1H), 7.24 3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, J =6H),  $3.09 (q_{AB}, J_{AB} = 15.6 \text{ Hz}, DV = 18.5 \text{ Hz}, 2H), <math>3.13$ -0.80-0.96 (m, 6H), 0.99-1.54 (m, 19H), 1.59-1.84 (m, (t, J = 7.5 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.56 (d, 1.5)3H), 2.09-2.24 (m, 1H), 2.45-2.58 (m, 2H), 2.81 (s, gave 0.8 g (73%) of 7 as a white foam. 'H NMR (CDCl,) d gradient containing.0.05% TFA (20-65% acetonitrile)

#### Example 1400

Step 1

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C14H13O2F fw=232.25

stirring, the layers were separated, and the organic After 15 h. refluxing, the mixture was cooled to room chloride (783.0g/5.000mol) in toluene (750 mL) was layer was extracted with a solution of potassium temperature and poured into  $H_2O$  (2.5 L). After 20 min. added via addition funnel while maintaining reflux. reflux (100 C) for lh. A solution of 3-methoxybenzyl period of 2.5 h. The reaction mixture was heated to in toluene (2.5 L) was added via addition funnel over a to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) toluene (2.5 L) was added, and the mixture was cooled and an addition funnel. The system was purged with  $N_2$ reflux condenser, N2 gas adaptor, mechanical stirrer, A 12-liter, 4-neck round-bottom flask was equipped with A slurry of sodium hydride (126.0g/4.988mol) in

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+ H) + = 233] confirmed desired structure. yield). b.p.: 120-130 C/50mtorrHg. distillation to give a clear, colorless oil (449.0g/39% vacuo. The crude product was purified by Kugelrohr ether, dried (MgSO<sub>4</sub>), filtered and concentrated in acidic solution was extracted three times with ethyl were combined and acidified with concentrated HCl. The extracted with 20% aq. KOH. All 20% aq. KOH solutions washed 5 times with toluene. The toluene washes were mixture was stirred for 30 min. The mixture was then added to 20% aqueous potassium hydroxide, and the hydroxide (720g) in. MeOH (2.5 L). The MeOH layer was 1H NMR and MS [ (M

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C<sub>17</sub>H<sub>18</sub>NO<sub>2</sub>FS fw=319.39

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The solution was cooled to 6 C, and sodium hydride purged with  $N_2$ . 4-Fluoro-2-(3-methoxybenzyl)-phenol A 12-liter, 3-neck round-bottom flask was fitted with  $(MgSO_4)$ , filtered, and concentrated in vacuo to give were washed with  ${
m H}_2{
m O}$  and saturated aqueous NaCl, dried times with ethyl ether. The combined organic layers mixture was poured into  $H_2O$  (4.0 L), and extracted two (55.5g/2.197mol) was added slowly. After warming to mechanical stirrer and  $N_2$  gas adaptor. The system was (242.4g/1.961mol) was added. After 15 h, the reaction room temperature, dimethylthiocarbamoyl chloride (455.5g/1.961mol) and dimethylformamide were added

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the product (605.3g, 97% yield). <sup>1</sup>H NMR and MS  $[(M+H)^+]$ = 320) confirm desired structure.

Step 3

C14H13OFS fw=248.32

A 12-liter, round-bottom flask was equipped with  $N_{
m 2}$  gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with  $N_2$ . 4-Fluoro-2-(3-

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concentrated in vacuo to give an amber oil (463.0g, 98sthydroxide (425.9g/7.590mol) was added, and the mixture with concentrated HCl, and extracted with ethyl ether. (605.3g/1.895mol) and phenyl ether (2.0kg) were added, mixture was stirred for 64 h. at room temparature and The ether extracts were dried (MgSO,), filtered, and then heated to reflux for 2 h. After cooling to room emperature, MeOH (2.0 L) and THF (2.0 L) were added, was heated to reflux for 4 h. After cooling to room emparature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with 120. The aqueous extracts were combined, acidified and the solution was heated to reflux for 2 h. The and the solution was stirred for 15 h. Potassium rield). 1H NMR confirmed desired structure. methoxybenzyl) -phenyldimethylthiocarbamate

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Step 4

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C25H35O2FS fw=418.61

A 5-liter, 3-neck, round-bottom flask was equipped with Sodium hydride (9.68g/383.2mmol) was added slowly, and dissolved in  $H_2O$ . The aqueous solution was washed with ether. The ether solution was dried  $({\rm MgSO}_4)$ , filtered, N2 gas adaptor and mechanical stirrer. The system was thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C. and conc'd in vacuo to give an amber oil (143.94g/85% cooled to room temperature, and extracted with ethyl 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was the mixture was allowed to warm to room temparature, ethyl ether, and concentrated  $H_2 SO_4$  was added. The yield). <sup>1</sup>H NMR and MS ( $(M + H)^+ = 419$ ) confirm the added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and aqueous solution was heated to reflux for 30 min, purged with N2. 4-Fluoro-2-(3-methoxybenzyl)desired structure.

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Step 5

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C25H33O2FS fw=416.59

confirm the desired structure. concentrated in vacuo to give a dark yellow-red oil silica gel, washing with  $ext{CH}_2 ext{Cl}_2$ . The filtrate was cooled to 0 C. Pyridinium chlorochromate  $N_{
m 2}$  gas adaptor, and mechanical stirrer. The system was A 2-liter, 4-neck, round-bottom flask was equipped with (110.6g, 77% yield). <sup>1</sup>H NMR and MS [(M + H)<sup>+</sup> = 417] added. After 20 min, the mixture was filtered through (143.94g/343.8mmol) and  $CH_2Cl_2$  (1.0 L) were added and purged with  ${
m N}_2$ . The corresponding alcohol (140.53g/651.6mmol) was added. After 6 h.,  $\mathrm{CH_2Cl_2}$  was

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Step 6

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C25H33O4FS fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with  $m N_2$  gas adaptor and mechanical stirrer. The system was

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ethyl ether. The organic layers were combined, dried  $\kappa_2 \text{CO}_3$ . An emulsion formed which was extracted with min, the reaction mixture was allowed to warm to room solution was cooled to 0 C, and 3-chloroperbenzoic acid purged with  ${
m N}_2$ . The corresponding sulfide desired structure. the product (93.2g, 78% yield). 1H NMR confirmed the  $(MgSO_4)$ , filtered, and concentrated in vacuo to give funnel. cooled to 0 C and filtered through a fine fritted temperature After 3.5 h, the reaction mixture was (158.21g/531.7mmol) was added portionwise. After 30 (110.6g/265.5mmol) and  $\mathrm{CH_2Cl_2}$  (1.0 L) were added. The The filtrate was washed with 10% aqueous

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Step 7

C25H33O4FS fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with via addition funnel. After 1h, 10% ag/ HCl (1.0 L) was The crude product was purified corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) by recryst. from 80/20 hexane/ethyl acetate to give a addition funnel. The system was purged with N2. The Potassium tert-butoxide (23.35g/208.1mmol) was added times with ethyl ether, dried  $(MgSO_4)$ , filtered, and toluene/ethyl acetate to give a white solid (33.60g/ combined yield: 71%). 1H NMR confirmed the desired added. After 1 h, the mixture was extracted three concentrated in vacuo and recrystelized from 95/5  $N_2$  gas adaptor, mechanical stirrer, and a powder were added, and the mixture was cooled to 0 C. white solid (32.18 g). The mother liquor was concentrated in vacuo. product.

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Step 8

C27H3904NS fw=473.67

CO2/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was The allowed to cool and was dissolved in ethyl ether. The vacuo to give a white solid (28.5g/96% yield). 1H NMR heated to 60 C. After 20 h, the reaction mixture was ether solution was washed with H2O, saturated aqueous added, and the vessel was sealed and cooled to -78 C. A Fisher porter bottle was fitted with  $N_2$  line and corresponding fluoro-compound (28.1g/62.6mmol) was. NaCl, dried (MgSO $_4$ ), filtered, and concentrated in Dimethylamine (17.1g/379mmol) was condensed via a magnetic stirrer. The system was purged with Nz. confirmed the desired structure.

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Step 9

C26H37O4NS fw=459.64

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give the product (6.27g/98% yield). IH NMR confirmed dried (MgSO<sub>d</sub>), filtered, and concentrated in vacuo to times with ethyl ether. The CHCl3 and ether extracts were combined, washed with saturated aqueous NaCl, separated, and the aqueous layer was extracted two with 10%  $\kappa_2$ CO $_3$  (100 mL). After 10 min, the layers were reaction mixture was cooled to 0 C and was quenched was allowed to warm to room temperature After 4 h, the tribromide (10.50g/41.9mmol) was added. The mixture reaction mixture was cooled to -78 C, and boron purged with  $N_2$ .  $N_2$  gas adaptor and magnetic stirrer. The system was A 250-mL, 3-neck, round-bottom flask was equipped with the desired structure. (6.62g/14.0mmol) and CHCl<sub>3</sub> (150 mL) were added. The The corresponding methoxy-compound

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Step 10

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In a 250 ml single neck round bottom Flask with stir bar place 2- diethylamineoethyl chloride hydochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 mmol,4.12g), 34 ml dry ether and 34 ml of 1N KOH(aqueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium carbonate.

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In a separate 2-necked 250 ml round bottom flask with stir bar add sodium hydride (60% dispersion in mineral oil, 100 mg, 2.6 mmol) and 34 ml of DMF. Cool to ice temperature. Next add phenol product (previous step) 1.1 g (2.4 mmilomoles in 5 ml DMF and the ether solution prepared above. Heat to 40C for 3 days. The product which contained no starting material by TLC was diluted with ether and extracted with 1 portion of 5% NaOH, followed by water and then brine. The ether layer was dried over magnesium sulfate and isolated by removing ether by rotary evaporation (1.3 gms). The product may be further purified by chromatography (SiO2 99% ethyl acetate/1% NH4OH at 5ml/min.). Isolated yield: 0.78 g (mass spec , and H1 NMR)

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Step 11

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558.83 g/mole) and 1.6 gms iodoethane (10.02 mmol) was placed in 5 ml acetonitrile in a fischer-porter bottle The product from step 10 ( 0.57gms, 1.02 millimole fw solution and the resulting mixture was chilled. The desired product is isolated as a precipitate 0.7272 chloroform. Next ether was added to the chloroform evaporated to dryness and redissolved in 5 mls of and heated to 45 C for 3 days. The solution was gms. Mass spec M-I = 587.9 , H NMR).

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Example 1401

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Step 1

C14H13O2F fw=232.25

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A 12-liter, 4-neck round-bottom flask was equipped with

solutions were combined and acidified with concentrated in toluene (2.5 L) was added via addition funnel over a to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) temperature and poured into  $H_2O$  (2.5 L). After 20 min. concentrated in vacuo. The crude product was purified and an addition funnel. The system was purged with  $\mathsf{N}_2$ mixture was stirred for 30 min. The mixture was then nydroxide (720g) in MeOH (2.5 L). The MeOH layer was After 15 h. refluxing, the mixture was cooled to room washed 5 times with toluene. The toluene washes were coluene (2.5 L) was added, and the mixture was cooled reflux (100 C) for 1h. A solution of 3-methoxybenzyl reflux condenser,  $N_2$  gas adaptor, mechanical stirrer, stirring, the layers were separated, and the organic period of 2.5 h. The reaction mixture was heated to HCl. The acidic solution was extracted three times added via addition funnel while maintaining reflux. chloride (783.0g/5.000mol) in toluene (750 mL) was added to 20% aqueous potassium hydroxide, and the layer was extracted with a solution of potassium with ethyl ether, dried over  ${\rm MgSO}_4$ , filtered and A slurry of sodium hydride (126.0g/4.988mol) in extracted with 20% ag. KOH. All 20% agueous KOH

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by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. <sup>1</sup>H NMR and MS [(M + H)<sup>+</sup> = 233] confirmed desired structure.

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Step 2

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yield). <sup>1</sup>H NMR and MS [(M+H)<sup>+</sup> = 320] confirm desired concentrated in vacuo to give the product (605.3g, 97% aqueous NaCl, dried over  ${
m MgSO_4}$ , filtered, and organic layers were washed with  $H_2O$  and saturated extracted two times with ethyl ether. The combined reaction mixture was poured into  ${\rm H_2O}$  (4.0 L), and added. phenol (455.5g/1.961mol) and dimethylformamide were chloride (242.4g/1.961mol) was added. After 15 h, the warming to room temperature, dimethylthiocarbamoyl hydride (55.5g/2.197mol) was added slowly. After with mechanical stirrer and  $\mathrm{N}_2$  gas adaptor. The system was purged with  $N_2$ . 4-Fluoro-2-(3-methoxybenzyl)-A 12-liter, 3-neck round-bottom flask was fitted The solution was cooled to 6 C, and sodium

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Step 3

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C17H18NO2FS fw=319.39

C14H13OFS fw=248.32

10 15 20 condenser. The system was purged with N2. 4-Fluoro-2-N2 gas adaptor, mechanical stirrer, and reflux temperature, MeOH (2.0 L) and THF (2.0 L) were added. then heated to reflux for 2 h. After cooling to room mixture was stirred for 64 h. at room temperature and and the solution was heated to reflux for 2 h. The H2O. The aqueous extracts were combined, acidified dissolved in ethyl ether (1.0 L), and extracted with was heated to reflux for 4 h. After cooling to room hydroxide (425.9g/7.590mol) was added, and the mixture and the solution was stirred for 15 h. Potassium (605.3g/1.895mol) and phenyl ether (2.0kg) were added (3-methoxybenzyl)-phenyldimethylthiocarbamate concentrated in vacuo to give an amber oil (463.0g, 98% ether extracts were dried (MgSO,), filtered, and with conc. HCl, and extracted with ethyl ether. The temperature, the mixture was concentrated by rotavap yield). A 12-liter, round-bottom flask was equipped with 1H NMR confirmed desired structure.

Step 4

C25H35O2FS fw=418.61

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Sodium hydride (9.68g/383.2mmol) was added slowly, and dissolved in H2O. The aqueous solution was washed with A 5-liter, 3-neck, round-bottom flask was equipped with  $N_2$  gas adaptor and mechanical stirrer. The system concentrated in vacuo to give an amber oil (143.94g/85% thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C. ethyl ether, and conc.  ${\rm H}_2{\rm SO}_4$  was added. The aqueous 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was the mixture was allowed to warm to room temperature solution was heated to reflux for 30 min, cooled to yield). <sup>1</sup>H NMR and MS [(M + H)<sup>+</sup> = 419] confirm the room temperature, and extracted with ethyl ether. was purged with  $N_2$ . 4-Fluoro-2-(3-methoxybenzyl)added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and ether solution was dried  $(MgSO_4)$ , filtered, and desired structure.

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Step 5

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C25H33O2PS fw=416.59

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A 2-liter, 4-neck, round-bottom flask was equipped (143.94 g/343.8 mmol) and  $\mathrm{CH}_2\mathrm{Cl}_2$  (1.0 L) were added and added. After 20 min, the mixture was filtered through (140.53g/651.6mol) was added. After 6 h.,  $CH_2Cl_2$  was system was purged with N2. The corresponding alcohol (110.6g, 77% yield). <sup>1</sup>H NMR and MS  $((M + H)^{+} = 417)$ concentrated in vacuo to give a dark yellow-red oil silica gel, washing with CH2Cl2. The filtrate was with  $N_2$  gas adaptor, and mechanical stirrer. The cooled to 0 C. Pyridinium chlorochromate confirm the desired structure.

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Step 6

C25H33O4FS fw=448.59

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ethyl ether. The organic layers were combined, dried min, the reaction mixture was allowed to warm to room was purged with  $N_2$ . The corresponding sulfide with  $N_2$  gas adaptor and mechanical stirrer. The system desired structure. the product (93.2g, 78% yield).  $^{
m l}$ H NMR confirmed the  $(MgSO_4)$ , filtered, and concentrated in vacuo to give K2CO3. An emulsion formed which was extracted with funnel. The filtrate was washed with 10% aqueous cooled to 0 C and filtered through a fine fritted temperature After 3.5 h, the reaction mixture was (158.21g/531.7mmol) was added portionwise. After 30 solution was cooled to 0 C, and 3-chloroperbenzoic acid (110.6g/265.5mmol) and  $\mathrm{CH_2Cl_2}$  (1.0 L) were added. The A 2-liter, 4-neck, round-bottom flask was equipped

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C25H33O4FS fw=448.59

give a white solid (32.18g). The mother liquor was via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) with  $N_2$  gas adaptor, mechanical stirrer, and a powder combined yield: 71%). 1H NMR confirmed the desired concentrated in vacuo and recrystallized from 95/5 by recrystallized from 80/20 hexane/ethyl acetate to concentrated in vacuo. The crude product was purified times with ethyl ether, dried  $(MgSO_4)$ , filtered, and added. After 1 h, the mixture was extracted three Potassium tert-butoxide (23.35g/208.1mmol) was added were added, and the mixture was cooled to 0 C. addition funnel. The system was purged with  ${
m N}_2$ . toluene/ethyl acetate to give a white solid (33.60g A 2-liter, 4-neck, round-bottom flask was equipped The

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Step 8

C27H3904NS fw=473.67

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A Fisher porter bottle was fitted with N<sub>2</sub> line and mixture was allowed to warm to room temperature and was vacuo to give a white solid (28.5g/96% yield). 1H NMR magnetic stirrer. The system was purged with  $N_2$ . The allowed to cool and was dissolved in ethyl ether. The NaCl, dried over  $MgSO_d$ , filtered, and concentrated in ether solution was washed with H2O, saturated aqueous heated to 60 C. After 20 h, the reaction mixture was added, and the vessel was sealed and cooled to -78 C. corresponding fluoro-compound (28.1g/62.6mmol) was  $CO_2$ /acetone bath and added to the reaction vessel. Dimethylamine (17.1g/379mmol) was condensed via a confirmed the desired structure.

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Step 9

C26H37O4NS fw=459.64

with 10%  $\rm K_2CO_3$  (100 mL). After 10 min, the layers were was purged with N2. The corresponding methoxy-compound was allowed to warm to room temperature After 4 h, the A 250-mL, 3-neck, round-bottom flask was equipped with N2 gas adaptor and magnetic stirrer. The system dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo times with ethyl ether. The CHCl<sub>j</sub> and ether extracts tribromide (10.50g/41.9mmol) was added. The mixture (6.62g/14.0mmol) and CHCl3 (150 mL) were added. The reaction mixture was cooled to 0 C and was quenched separated, and the aqueous layer was extracted two were combined, washed with saturated aqueous NaCl, reaction mixture was cooled to -78 C, and boron to give the product (6.27g/98% yield). 1H NMR confirmed the desired structure.

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Step 11

Step 10

millimoles, 4.12g), 34 ml dry ether and 34 ml of 1N KOH extraction and dry over anhydrous potassium carbonate hydochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 stir bar place 2- diethylamineoethyl chloride (aqueous). Stir 15 minutes and then separate by ether In a 250 ml single neck round bottom flask with

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mineral oil, 100 mg, (2.6 mmol) and 34 ml of DMF. Cool Isolated yield: 0.78 g (mass spec , and H1 NMR) product may be further purified by chromatography was dried over Magnesium sulfate and isolated by NaOH, followed by water and then brine. The ether layer diluted with ether and extracted with 1 portion of 5% product which contained no starting material by TLC was solution prepared above. Heat to 40C for 3 days. The step) 1.1 g (2.4 mmol in 5 ml DMF and the ether to ice temperature. Next add phenol product (previous with stir bar add sodium hydride (60% dispersion in (silica 99% ethyl acetate/1% NH4OH at 5ml/min.). removing ether by rotary evaporation (1.3 gms). The In a separate 2-necked 250 ml round bottom flask

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precipitate 0.7272 gms. Mass spec M-I = 587.9, <sup>1</sup>H chilled. The desired product is isolated as a mls of chloroform. Next ether was added to the mmilimoles) was place in 5 ml acetonitrile in a Fischerchloroform solution and the resulting mixture was solution was evaporated to dryness and redissolved in 5 fw 558.83 g/mole) and iodoethane (1.6 gms (10.02 Porter bottle and heated to 45 C for 3 days. The The product from step 10 (0.57gms, 1.02 millimole

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BIOLOGICAL ASSAYS

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essentially using a procedure recognized to show the assays are performed in vitro and in animal models invention is shown by the following assays. These utility of the present invention. The utility of the compounds of the present

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untake of ["C]-Taurocholate (TC) in H16 Colle In Vitro Assay of compounds that inhibit IBAT-modiated

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the cDNA of human IBAT (H14 cells) are seeded at 60,000 Baby hamster kidney cells (BHK) transfected with

cells/well in 96 well Top-Count tissue culture plates cells/well for assays run within 48 hours, and 10,000 for assays run within in 24 hours of seeding, 30,000 cells/well for assays run within 72 hours.

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compound in assay buffer is added along with 50 ml of 6 the plates are heat sealed and shaken for 30 minutes at 200 ml of liquid scintillation counting fluid is added, 0.2% (w/v) (PAF)BSA. The wells are then gently washed On the day of assay, the cell monolayer is gently (w/v) fatty acid free bovine serum albumin- (FAF)BSA). culture plates are incubated 2 hours at 37°C prior to To each well 50 ml of a two-fold concentrate of test Dulbecco's phosphate-buffered saline (PBS) containing once with 100 ml 4° C PBS without (FAP)BSA. To each Modified Eagle's medium with 4.5 g/L glucose + 0.2% concentration of 3 mM ["C]-taurocholate). The cell room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count washed once with 100 ml assay buffer (Dulbecco's gently washing each well twice with 100 ml 4°C mM ["C]-taurocholate in assay buffer (final instrument.

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["Cl-Alanine

In Vitro Assay of compounds that inhibit uptake of

identical fashion to the taurocholate assay, with the exception that labeled alanine is substituted for the The alanine uptake assay is performed in an labeled taurocholate.

In Vivo Assay of compounds that inhibit Rat Iloni uptake of ["Cl-Taurocholate into Bile

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cholanoic acid in hamsters" in Biochimica et Biophysica (See Metabolism of 3a,7b-dihydroxy-7a-methyl-5bcholanoic acid and 3a,7b-dihydroxy-7a-methyl-5b-Acta 833 (1985) 196-202 by Une et al.)

Male wistar rats (200-300 g) are anesthetized with luer lock, tapered female adapter) is inserted at 12 cm of control sample (["C]-taurocholate @ 0.05 mi/ml with from the junction of the small intestine and the cecum. 5 mM cold taurocholate) is loaded into the gut segment inactin 0100 mg/kg. Bile ducts are cannulated with a opening is cannulated with a 20 cm length of silicone continuously. At the start of the experiment, 2.0 ml Dulbecco's phosphate buffered saline, pH 6.5 (PBS) is exposed and laid out on a gauze pad. A canulae (1/8" collected every 3 minute for the first 27 minutes of used to flush out the intestine segment. The distal intestine is washed for 20 min with warm PBS at 0.25 ml/min. Temperature of the gut segment is monitored the procedure. After the 21 min of sample infusion, cannulae is hooked up to a peristaltic pump and the begun. Control sample is infused at a rate of 0.25 10" length of PE10 tubing. The small intestine is (utilizing a 8 cm length of ileum). 20 ml of warm with a 3 ml syringe and bile sample collection is tubing (0.02" I.D. x 0.037" 0.D.). The proximal A slit is cut at 4 cm from this same junction ml/min for 21 min. Bile samples fractions are

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the ileal loop is washed out with 20 ml of warm PBS

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typically contains the control sample. necessary, a third perfusion is performed as above that sampled every 3 min for the first 27 min. administration followed by 21 min of wash out) and bile perfusion is initiated as described above but this with test compound being administered as well (21 min out for 21 min with warm PBS at 0.25 ml/min. A second (using a 30 ml syringe), and then the loop is washed

#### Measurgment of Hematic Cholestorol Concentration (HEPATIC CHOL)

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et al. (1974) Clin. Chem. 20, 470. oxidase and peroxidase, as described by Allain, C. A., enzymatically, using a combination of cholesterol under nitrogen. The residue was dissolved in centrifugation the supernatant was separated and dried chloroform:methanol (2:1). After homogenization and isopropanol and the cholesterol content was measured Liver tissue was weighed and homogenized in

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# Moscuromont of Reputle ENG CoA-Reductage Activity (HNG

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radioactivity was determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) J. enzyme product was scraped off the plate, extracted and chromatography, and the spot corresponding to the supernatant was separated, by thin-layer followed by centrifugation. An aliquot of the NEN). The reaction was stopped by adding 6N HCl minutes at 37° C in the presence of "C-HMG-CoA (Dupontby centrifugal separation. The final pelleted material *Lipid Res.* **31**, 2159). for HMG CoA reductase activity by incubating for 60 was resuspended in buffer and an aliquot was assayed liver samples in a phosphate/sucrose buffer, followed Hepatic microsomes were prepared by homogenizing

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# Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL,

Catalog No. 337-B. VLDL and LDL (VLDL + LDL) with Sigma Chemical Co. HDL Cholesterol reagent, difference between total and HDL cholesterol. cholesterol concentrations were calculated as the enzymatically with Sigma Chemical Co. GPO-Trinder, serum triglycerides (blanked) (TGI) were assayed Catalog No. 352-3 (dextran sulfate method). Total using this same kit after precipitation of VLDL and LDL 276-64909. HDL cholesterol (HDL-CHOL) was assayed Chemicals (Richmond, VA); Cholesterol C11, Catalog No. enzymatically using a commercial kit from Wako Fine Total serum cholesterol (SER.CHOL) was measured

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### Activity (7a-OHaso) Mosgursment of Repatic Cholesterol 7-a-Hydromylago

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eluted material using UV detection at 240nm. separated by injecting an aliquot of the extract onto solvent was evaporated and the residue was dissolved in Following extraction into petroleum ether, the organic for 5 minutes at 37° C in the presence of NADPH. by centrifugal separation. The final pelleted material C, reversed phase HPLC column and quantitating the acetonitrile/ methanol. The enzymatic product was for cholesterol 7-a-hydroxylase activity by incubating was resuspended in buffer and an aliquot was assayed liver samples in a phosphate/sucrose buffer, followed (Reference: Horton, J. D., et al. (1994) J. Clin Invest. 93, 2084). Hepatic microsomes were prepared by homogenizing

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## Measurement of Fecal Bile Acid Concentration (FRA)

a stream of nitrogen, pulverized and weighed. hamsters was collected for 24 or 48 hours, dried under Approximately 0.1 gram was weighed out and extracted Total fecal output from individually housed

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into an organic solvent (butanol/water). Following separation and drying, the residue was dissolved in methanol and the amount of bile acid present was measured enzymatically using the 3a-hydroxysteroid steroid dehydrogenase reaction with bile acids to

reduce NAD. (Reference: Mashige, F., et al. (1981)

Clin. Chem. 27, 1352).

### L'alteurocholato Untake in Rabbit Brush Bordor Membrano Yosiclor (BERV)

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ncubated for 5 sec with 10 µl of brush border membrane and the reaction was stopped by the addition of 5 ml of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed Rabbit Ileal brush border membranes were prepared instead of 100 µl. Briefly, at room temperature a 190 Biochimica Biophysica Acta, 556, 259). The method for measuring taurocholate was essentially as described by Kramer et al. (Reference: (1992) Biochimica Biophysica um pore) and an additional 5 ml wash with stop buffer. ul solution containing 2µM ('H]-taurocholate(0.75 µCi) from frozen ileal mucosa by the calcium precipitation initiated by the addition of the BBMV while vortexing immediately by filtration through a nylon filter (0.2 method describe by Malathi et al. "(Reference: (1979) 20 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 was Acta, 1111, 93) except the assay volume was 200 µl resicles (60-120 µg protein). The incubation was

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### Acvi-Colicholosterol Acvi Transferase (ACAT)

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Hamster liver and rat intestinal microsomes were prepared from tissue as described previously (Reference: (1980) J. Biol. Chem. 255, 9098) and used as a source of ACAT enzyme. The assay consisted of a 2.0 ml incubation containing 24 µM Oleoyl-CoA (0.05 µCi) in a 50 mM sodium phosphate, 2 mM DTT ph 7.4 buffer containing 0.25 % BSA and 200 µg of microsomal

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protein. The assay was initiated by the addition of oleoyl-CoA. The reaction went for 5 min at 37° C and was terminated by the addition of 8.0 ml of chloroform/methanol (2:1). To the extraction was added 125 µg of cholesterol oleate in chloroform methanol to act as a carrier and the organic and aqueous phases of the extraction were separated by centrifugation after thorough vortexing. The chloroform phase was taken to dryness and then spotted on a silica gel 60 TLC plate and developed in hexane/ethyl ether (9:1). The amount of cholesterol ester formed was determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the TLC plate with a Packard

Data from each of the noted compounds in the assays described above is as set forth in TABLES 5, 6, 7, and 8 as follows:

instaimager.

TABLE 5

6a	Mixture of 9a and 9b	8a and 8b	8a	19b	19a	15	13	148	14b	18	4b	5b	5a	4a .	3	12	pine=	Benzothiaze					COMPOUND
5	6					60						40		•				2				r.M.	IC50
		69	41	15	0		23	13	18	6	9		34	3	0	25			100 uM #	Uptake @	of TC	Inhibition	In vitro &
												0						0	100 uM #	Uptake @	of Alanine	Inhibition	æ
												72.9 ± 5.4 @ 0.5 mM						45.4 +/- 0.7			@ O.1	Transport of TC in	% of Control

37	31	30	29	28	27	Č	25	10b	10a	7	17		6d	6c	216	21c	21a	6d and 10a	Mixture of	Mixture of	9a	99
<b>ω</b>				8	5		0:1	15	7	50			0.6	2					0.8	13	5	
	41 @ 50 mM	96 @ 50 mM	88 @ 50 mM								10				45	52	37					. 58
0% 0 5 mM				31% @ 20mM	7% 0 20 mM	MM 25	9	68.6	77.6	49.3			77.7	58.5		•		MIM	148 @ 25		0% @ 25 mM	
						87.9 +/- 1.5	26.0 +/- 3.3		62.4 =/- 2.5 @ 0.2 mM		•	0.2 +/- 0.9 mM	16.1 +/- 1.1 0 0.5	68.8 +/- 5.7 at 0.4 mM							53.7 +/- 3.9	

		_			τ		_	_	_	_	_	1		_
20.6 +/- 5.7						21.2 +/- 2.7								
11% @ 5mM		08 @ 20 mM		16% @ 25 mM	22% @ 20 mM	21% @ 200 mM				65	175			
	49 @ 50 mM						S1 @ 50 mM	20 @ 50 mM					90 G mm	100 @ 6 шМ
0.3		2 .	1.5	1.5	2	0.15			70	6	30	ខ្ន		
38	40	41	42	43	48	49	57	. 85	59	09	61	62	63	64

• In vitro Taurocholate Cell Uptake # Unless otherwise noted = Comparative Example 1s Example No. 1 in WO 93/16055

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#### TABLE 6

1118) LOOP 1C(50) EC(5) 1 mM 74 0.6 mM 31 0.3 mM 12
0.1 mM 0.1 mM

## Comparative Example is Example No. 1 in WO 93/16055

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TABLE 7			
EFFICACY OF COMPOUND NO. 25 IN CHOLESTEROL-FED HAMSTERS	IND NO. 25 IN	CHOLESTEROL-FE	ED HAMSTERS
Parameter	CONTROL	4% CHOLES- TYRAMINE	0.2% CPD. NO. 25
WEIGHT (G)	(mean ± SEM, Dunnett's)	(mean ± SEM, *p<0.05, A-Student's t, B- Dunnett's)	udent's t, B-
day 1	117	114(6)	117(5)
day 14	(2)	127 (3)	132 (4)
LIVER WEIGHT (G)	127 (3	4.9(0.4	5.8(0.2)
SER.CHOL(mg%)	_	_	126(2)*A
HDL-CHOL (mg%)	5.4(0	119 (4) *	B,
VLDL + LDL	.3)	A,B	76(1) *A,
TGI (mg%)	143(7	76(3)*A	Ø

		.8)	1
		6.2(0	
	5) *A, B	.1)	
)*A,B	12.3(1.	2.3(0	
11.9(0.5	) *A,B	_	
_	2.7(0.1	235.3(25.1	
2.4(0.04	8.3) *A,B		
0)*A	357.2(2	7.6)	
291.0(6.		15.8(	
	1.6) *A,B	.3)	
Ì	448.8(2	2.5(0	PBA (mM/24H/100g)
312.9(37.5)*A	)*A,B	2)	24 HR. FECAL Wt (G)
*A,B	1.9(0.1	203 (3	7a-OHase (pm/mg/min.)
1.9(0.1)	190(15)	54 (7)	
175 (11)	42(3)*A	89(4)	HMG COA (pm/mg/min.)
50(3)	`₽	÷	HEPATIC CHOL (mg/g)

.8)	6.2(0	.1) 5)*A,B	2.3(0   12.3(1.  )*A	) *A, B	235.3(25.1 2.7(0.1 )	8.3)*A,B	. 7.6) 357.2(2 0)*.	15.8(	.3) 1.6)*A,B	FBA (mM/24H/100g) 2.5(0 448.8(2 ,B	24 HR. FECAL Wt (G) 2) )*A,B 312	7a-OHase (pm/mg/min.) 203(3 1.9(0.1 *A,	54(7) 190(15)	HMG CUA (pm/mg/min.) 89(4) 42(3)*A	
			3(1. )*A,B	11.9(0.5	(0.1 )	2.4(0.04	.2(2 0)*A	291.0(6.			312.9(37.5)*A	(0.1 *A,B	(15) 1.9(0.1)	3)*A 175(11)	

WEIGHT (G)

Dunnett's)

(mean ± SEM, \*p<0.05, A-Student's t, B-

CPD. NO. 25 20 MPL/DAY

day 8 day 1

330 (4) 307 (4)

310 (4)\*A,B

307 (3)

15.5 (0.6)

PARAMETER

CONTROL

TABLE 8

EFFICACY OF COMPOUND NO. 25 IN RAT ALZET MINIPUMP MODEL

conducted in Additional taurocholate uptake tests were FBA (mM/24H/100g) 24 HR. FECAL WT (G) 7a-OHase (pm/mg/min)

17.9 (0.9) 5.8 (0.1) 281.9 (13.9)

(35.7) \*A,B

5.7 (0.4) 39.1 (4.5)\*A,B

535.2

HMG COA pm/mg/min HEPATIC CHOL(mg/g) SER. CHOL (mg%) LIVER WEIGHT (G)

75.1 (6.4) 21 (0.03) 85 (3)

(40.7)\*A,B

318.0

2.0 (0.03) 84 (3) 14.6 (0.4)

the following compounds listed in Table 9.

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TABLE 9

Biological Assay Data for Some Compounds of the Present Invention

Alanine Uptake Percent Inhibition © µM	0@1.0		13 @ 0.25				14.0 @ 0.063		2.0 @ 0.063								12.0 @ 0.625			34.0 @ 5.0				14.0 @ 6.25		18 @ 1.25					5.4 @ 0.063				
Human TC IC <sub>50</sub> (μM)		0.083		0.0056	9.0	8.0		0.3		60:0	2.5	3.0	0.1	0.19	8.0	0.3		0.4	1.3		0.068	1.07	1.67		18.0		0.55	0.7	0.035	1.28		16.0	0.3	22.0	60.0
Compound Number	101	102	103	104	105	106	107	108	601	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	131	132	133	134	135	136

13/	2.4	
138	3.0	
139	>25.0	
142	0.5	
143	0.03	
144	0.053	
292	20.0	
263	0.7	
264	0.2	
265	2.0	
366	0.5	
267	0.073	
268	0.029	
269	80:0	
270	0.12	
271	0.07	ľ
272	0.7	
273	1.9	
274	0.18	
275	5.0	@ 0.25
276	0.23	
277	50.04	
278	3.0	
279	6.4	
280	0.18	
281	0.019	
282	0.021	
283	0.35	
284	0.08	
286	19.0	
287	4.0	
288	10.0	@ 6.25
289	0.23	
290	0.054	
291	0.6	
292	0.046	
293	1.9	
294	0.013	
295	1.3	
596	1.6	
1005	0.0004	
1006	0.001	

_	_		_	_	_	_		_		_	_	_	_	_	_		_	_	_	_		_		_				_													
1090	1089	1088	1087	1086	1085	1084	1083	1082	1081	1080	1079	1078	1077	1076	1075	1074	1073	1072	1071	1070	1069	1068	1067	1066	1065	1064	1063	1062	1061	1060	1059	1058	1057	1056	1055	1054	1053	1052	1051	1050	1049
0.006	0.0057	0.0055	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.0045	0.0045	0.0045	0.0043	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.0036	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
							•																																		

0.003	1048
0.003	1047
0.003	1046
0.003	1045
0.003	1044
0.003	1043
0.003	1042
0.003	1041
0.003	1040
0.0026	1039
0.0025	1038
0.0022	1037
0.002	1036
0.002	1035
0.002	1034
0.002	1033
0.002	1032
0.002	1031
0.002	1030
0.002	1029
0.002	1028
0.002	1027
0.002	1026
0.002	1025
0.002	1024
0.002	1023
0.002	1022
0.002	1021
0.002	1020
0.002	1019
0.002	1018
0.002	1017
0.002	1016
0.002	1015
0.002	1014
0.002	1013
0.0015	1012
0.001	1011
0.001	1010
0.001	1009 ·
0.001	1008
0.001	1007

339

0.000	90:0	9000	9000	0.006	9000	9000	900:0	0.0063	0.0068	0.007	0.007	200.0	0.007	0.007	0.0073	0.0075	0.0075	0.008	0.008	0.008	0.008	0.009	600.0	8600:0	0.0093	0.01	0.01	0.01	0.01	0.01	0.011	0.011	0.011	0.012	0.013	0.013	0.017	0.018	0.018	0.02
1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	=======================================	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131

0.02	0.02	0.021	0.021	0.021	0.022	0.022	0.023	0.023	0.024	0.027	0.028	0.029	0.029	0.029	0.03	0.03	0.03	0.031	0.036	0.037	0.037	0.039	0.039	0.04	90.0	90.0	0.062	0.063	0.063	0:09	0.093	0.11	0.11	0.12	0.12	0.12	0.13	0.14	0.14	0.15	0.15
1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174

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0 @ 0.063

0.05 0.034 0.035 0.042

0 @ 0.063

0.032 0.041 0.025 0.045 0.065 0.

16.5	0.012	0.019	0.03	6.000	0.21	0.24	0.2	0.29	0.035	0.026	0.026	0.011	0.047	0.029	0.028	0.024	0.029	0.018	0.017	0.028	0.76	0.055	0.17	0.17	0.011	0.027	0.068	0.071	0.013	0.026	0.017	0.013	0.025	0.019	0.011	0.014	0.063	0.029	0.018	0.012	1.0
1259	1260	1261	1262	1263	1264	1265	1266	1267	1268	1269	1270	1271	1272	1273	1274	1275	1276	1277	1278	1279	1280	1281	1282	1283	1284	1285	1286	1287	1288	1289	1290	1291	1292	1293	1294	1295	1296	1297	1298	1299	1300

1301	0.15	
1302	7.00	
1300	0.26	
1304	0.25	
1305	0.25	
1306	1.2	
1307	3.1	
1308	0.04	
1309	0.24	
1310	1.16	
1311	3.27	
1312	5.0	
1313	6.1	
1314	0.26	
1315	1.67	
1316	3.9	
1317	21.0	
1319		11.0 @ 0.25
1321		11.1@5.0
1322		3.0 @ 0.0063
. 1323		4.0 @ 0.0063
1324		43.0 @ 0.0008
1325		1.0 @ 0.0063
1326		0
1327		3.0 @ 0.0063
1328		
1329		(3)
1330		3
1331		3
1332		43.0 @ 0.0008
1333		0 @ 0.0063
1334	Į,	3
1335		38.0 @ 0.0008
1336		45.0 @ 0.0008
1337		0 @ 0.0063
1338		1.0 @ 0.25
1339		0 @ 0.063
1340		9.0 @ 0.063
.1341		1.0 @ 0.063
1342		➂
1345		13.0 @ 0.25
1347	0.0036	

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1451	1450	1449	1375	1374	1373	1372	1371	1370	1369	1368	1367	1366	1365	1364	1363	1362	1361	1360	1359	1358	1357	1356	1355	1354	1353	1352	1001
0.014	0.039	0.052	0.002	0.007	0.008	0.004	0.004	0.002	0.005	0.005	0.002	0.015	0.008	0.006	0.008	0.019	0.004	0.003	0.014	0.008	0.023	0.22	0.0015	0.006	0.0015	0.10	0.44

The examples herein can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

Novel compositions of the invention are further illustrated in attached Exhibits A and B.

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The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

Table C2: Alternative compounds #2 (Families F101-F123)

Family Cpd#	Cpd# R1=R2	R <sup>5</sup>	(R*) q
F101	CHOSEN FROM TABLE D*	Ph-	CHOSEN FROM TABLE D
F102	CHOSEN FROM TABLE D	p-F-ph-	CHOSEN FROM TABLE D
F103	CHOSEN FROM TABLE D	n-F-Ph-	CHOSEN FROM TABLE D
F104	CHOSEN FROM TABLE D	p-CH <sub>3</sub> O-Ph-	CHOSEN FROM TABLE D
F105	CHOSEN FROM TABLE D	m-CH3O-Ph-	CHOSEN FROM TABLE D
F106	CHOSEN FROM TABLE D	p- (CH <sub>3</sub> ) <sub>2</sub> N-Ph-	CHOSEN FROM TABLE D
F107	CHOSEN FROM TABLE D	n- (CH <sub>3</sub> ) <sub>2</sub> N-Ph	CHOSEN FROM TABLE D
F108	CHOSEN FROM TABLE D	I <sup>-</sup> , p-(CH <sub>3</sub> ) <sub>3</sub> -N <sup>+</sup> -Ph-	CHOSEN FROM TABLE D
F109	CHOSEN FROM TABLE D	I-, m-(CH3)3-N+-Ph-	CHOSEN FROM TABLE D
F110	CHOSEN FROM TABLE D	I <sup>-</sup> , p-(CH <sub>3</sub> ) <sub>3</sub> -N <sup>+</sup> -CH <sub>2</sub> CH <sub>2</sub> - (OCH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> -O-Ph-	CHOSEN FROM TABLE D
F111	CHOSEN FROM TABLE D	I-, m-(CH <sub>3</sub> ) <sub>3</sub> -N*-CH <sub>2</sub> CH <sub>2</sub> - (OCH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> -O-Ph-	CHOSEN FROM TABLE D
F112	CHOSEN FROM TABLE D	I <sup>-</sup> , p-(N,N- dimethylpiperazine)-(N')- CH2-(OCH2CH2)2-O-Ph-	CHOSEN FROM TABLE D

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CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM
TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D
I', m-(N,N- dimethylpiperazine)-(N')- CH2-(OCH2CH2)2-O-Ph-	m-F-Ph- p-CH <sub>3</sub> O-	3,4,dioxy-methylene-Ph-	A-F-Ph- p-F-Ph-	м-СН <sub>3</sub> О- р-Е-Рh-	4-pyridine	N-methyl-4-pyridinium	3-pyridine	N-methyl-3-pyridinium	2-pyridine	p-CH3O2C-Ph-
CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM	CHOSEN FROM
TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D	TABLE D
F113	F114	F115	F116	F117	F118	F119	F120	F121	F122	F123

Similar families can be generated where  $R^1<>R^2$ , such as  $R^1$  = Et and  $R^2$  = n-Bu, but (R\*)q is chosen from table C1.

OH BU

A compound of formula (I):

E

q is an integer from 1 to 4;

n is an integer from 0 to 2;

haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,  $\rm R^1$  and  $\rm R^2$  are independently selected from the group consisting of H, alkyl, alkenyl, alkymyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

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NR<sup>9</sup>R<sup>10</sup>, N'R'R"R"A', SR<sup>9</sup>, S'R'A-. P'R'R"'R"A', S(0)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of  $\mathtt{OR}^9$ wherein alkyl, alkenyl, alkynyl, haloalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,

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N<sup>+R9</sup>R<sup>10</sup>A-, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>9</sup>A-, P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, or phenylene, optionally have one or more carbons replaced by 0,  $\ensuremath{\mathrm{NR}}^9$ alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl wherein alkyl, alkenyl, alkynyl, alkylaryl, SO3R9, CO2R9, CN, halogen, oxo, and CONR9R10,

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wherein  $\mathrm{R}^9$  ,  $\mathrm{R}^{10}$  , and  $\mathrm{R}^{\text{W}}$  are independently selected ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; or from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle,

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they are attached form C,-C, cycloalkylidene;  $\mathrm{R}^{1}$  and  $\mathrm{R}^{2}$  taken together with the carbon to which

SO2R , and SO3R , wherein R and R are as defined acyloxy, aryl, heterocycle, oR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, SR<sup>9</sup>, S(0)R<sup>9</sup> group consisting of H, alkyl, alkenyl, alkynyl,  ${ t R}^3$  and  ${ t R}^4$  are independently selected from the

, or =CR<sup>11</sup>R<sup>12</sup>  ${
m R}^3$  and  ${
m R}^4$  together form =0, =NOR $^{11}$ , =S, =NNR $^{11}{
m R}^{12}$ 

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both  $R^3$  and  $R^4$  cannot be OH, NH2, and SH, or wherein  ${ t R}^9$  and  ${ t R}^{10}$  are as defined above, provided that SO2R9, SO3R9, CO2R9, CN, halogen, oxo, and CONR9R10 cycloalkyl, cyanoalkyl, OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, SR<sup>9</sup>, S(O)R<sup>9</sup> heterocycle, carboxyalkyl, carboalkoxyalkyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, from the group consisting of H, alkyl, alkenyl, wherein  $R^{11}$  and  $R^{12}$  are independently selected

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atom to which they are attached form a cyclic ring;  $_{
m R}^{11}$  and  $_{
m R}^{12}$  together with the nitrogen or carbon

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cycloalkyl, heterocycle, quaternary heterocycle, OR9 group consisting of H, alkyl, alkenyl, alkynyl, aryl,  $SR^9$ ,  $S(O)R^9$ ,  $SO_2R^9$ , and  $SO_3R^9$  ${ t R}^{ extsf{5}}$  and  ${ t R}^{ extsf{6}}$  are independently selected from the

SO2R 13, SO3R 13, NR 13 OR 14, NR 13 NR 14 R 15, NO2, CO2R 13, CN, arylalkyl, quaternary heterocycle, quaternary group consisting of alkyl, alkenyl, alkynyl, polyalkyl, substituent groups independently selected from the OM, SO2OM, SO2NR $^{13}$ R $^{14}$ , C(O)NR $^{13}$ R $^{14}$ , C(O)OM, COR $^{13}$ heteroaryl, halogen, oxo,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(O)R^{13}$ polyether, aryl, haloalkyl, cycloalkyl, heterocycle, heteroaryl can be substituted with one or more heterocycle, quaternary heterocycle, and quaternary wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl

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N+R9R11R12A-, P(0)R<sup>13</sup>R<sup>14</sup>, P\*R<sup>13</sup>R<sup>14</sup>R15A-, P(0R")OR", S'R"R"A', and

a pharmaceutically acceptable cation,  $\mathtt{A}^-$  is a pharmaceutically acceptable anion and M is said alkyl, alkenyl, alkynyl, polyalkyl,

 $conr^7 R^8$ ,  $N^+ R^7 R^8 R^9 A^-$ , alkyl, alkenyl, alkynyl, aryl,  $NR^{7}R^{8}$ ,  $SR^{7}$ ,  $S(0)R^{7}$ ,  $SO_{2}R^{7}$ ,  $SO_{3}R^{7}$ ,  $CO_{2}R^{7}$ , CN, OXO, cycloalkyl, heterocycle, arylalkyl, quaternary groups selected from the group consisting of OR7, can be further substituted with one or more substituent polyether, aryl, haloalkyl, cycloalkyl, and heterocycle heterocycle, quaternary heteroaryl,  $P(0)R^7R^8$ 

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polyether, aryl, haloalkyl, cycloalkyl, and heterocycle  $P^{\dagger}R^{7}R^{8}R^{9}A^{-}$ , and  $P(0)(OR^{7})OR^{8}$ , and wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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NR, N+R, RA-, S, SO, SO2, S+R, A-, PR, P(0)R7, can optionally have one or more carbons replaced by O,

quaternary heteroarylalkyl, quaternary heterocycle, quaternary heteroaryl, and arylalkyl, cycloalkyl, heterocycle, heterocycle, hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl,  $P^{+}R^{7}R^{8}A^{-}$ , or phenylene, and  $R^{13}$ ,  $R^{14}$ , and  $R^{15}$  are independently selected from the group consisting of

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 $S^{+}R^{9}A^{-}$ ,  $PR^{9}$ ,  $P^{+}R^{9}R^{10}A^{-}$ ,  $P(0)R^{*}$ , phenylene, carbohydrate carbons replaced by 0, NR',  $N^+R^9R^{10}A_-$ , S, S0, S02 heterocycle, and polyalkyl optionally have one or more wherein alkyl, alkenyl, alkynyl, arylalkyl,

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of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>9</sup>, S(0)R<sup>9</sup> one or more groups selected from the group consisting  $m R^{13}$  ,  $m R^{14}$  , and  $m R^{15}$  are optionally substituted with

amino acid, peptide, or polypeptide, and

SO2R<sup>9</sup>, SO3R<sup>9</sup>, oxo, CO2R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO2OM, SO2NR<sup>9</sup>R<sup>10</sup>, PO(OR16)OR17, P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, S<sup>+</sup>R<sup>9</sup>A-, and C(0)OM,

 $\cdot$   $R^{14}$  and  $R^{15}$  , together with the nitrogen atom to wherein  $R^{16}$  and  $R^{17}$  are independently selected from the substituents constituting R<sup>9</sup> and M; or which they are attached, form a cyclic ring;

 ${\mathtt R}^7$  and  ${\mathtt R}^8$  are independently selected from the group consisting of hydrogen and alkyl; and

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one or more  $\mathtt{R}^{\mathsf{X}}$  are independently selected from the SO3R<sup>13</sup>, S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A-, NR<sup>13</sup>OR<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, NO<sub>2</sub>, CO<sub>2</sub>R<sup>13</sup>,  $^{13}$  NR14C(0)R13, C(0)OM,  $^{13}$ ,  $^{16}$ ,  $^{18}$ ,  $^{1}$  S(0) $^{1}$  NR $^{18}$ ,  $^{18}$  NR $^{13}$ R $^{18}$ heteroaryl,  ${
m or}^{13}$ ,  ${
m NR}^{13}{
m R}^{14}$ ,  ${
m SR}^{13}$ ,  ${
m S(O)R}^{13}$ ,  ${
m S(O)}^{2}{
m R}^{13}$ , CN, OM,  $SO_2OM$ ,  $SO_2NR^{13}R^{14}$ ,  $NR^{"C}(O)R"$ ,  $C(O)NR^{13}R^{14}$ , NR<sup>18</sup>OR<sup>14</sup>, N\*R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, P\*R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, amino acid, haloalkyl, cycloalkyl, heterocycle, heterocycle, group consisting of H, alkyl, alkenyl, alkynyl, polyether, quaternary heterocycle, quaternary polyalkyl, acyloxy, aryl, arylalkyl, halogen, peptide, polypeptide, and carbohydrate,

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wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl heteroaryl can be further substituted with  $\mathtt{OR}^9$ ,  $\mathtt{NR}^9\mathtt{R}^{10}$ polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>9</sup>, S(0)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, SO<sub>3</sub>R<sup>9</sup>, oxo, CO<sub>2</sub>R<sup>9</sup>, CN, halogen,  ${\tt CONR}^9{\tt R}^{10}$ ,  ${\tt SO_2OM}$ ,  ${\tt SO_2NR}^9{\tt R}^{10}$ ,  ${\tt PO(OR")OR"}$ polyether, quaternary heterocycle, and quaternary P+R9R11R12A-, S'R'R'9A', or C(0)OM, and

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wherein  $R^{18}$  is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl,

heterocycle, heterocycle, alkyl quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituent selected from the group wherein acyl, arylalkoxycarbonyl, arylalkyl,

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SO2R<sup>9</sup>, SO3R<sup>9</sup>, oxo, 'CO2R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO3R<sup>9</sup> consisting of .OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>9</sup>, S(O)R<sup>9</sup>,  $\mathrm{So_2OM}$ ,  $\mathrm{So_2NR^9R^{10}}$ ,  $\mathrm{Po(OR^{16})OR^{17}}$ , and  $\mathrm{C(O)OM}$ , wherein in  $R^{\mathbf{X}}$ , one or more carbons are optionally replaced by 0, NR<sup>13</sup>, N<sup>\*</sup>R<sup>13</sup>R<sup>14</sup>A-, S, SO, SO<sub>2</sub>, S<sup>\*</sup>R<sup>13</sup>A-, peptide, polypeptide, carbohydrate, polyether, or PR<sup>13</sup>, P(O)R13, P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A-, phenylene, amino acid, polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, carbons are optionally replaced by 0,  $NR^9$ ,  $N^+R^9R^{10}A^-$ , peptide, polypeptide, and carbohydrate, one or more s, so, so2, s+R3A-, PR3, P+R3R10A-, or P(O)R1;

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haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, neteroaryl are optionally substituted with one or more P\*R13R14R15A-, P(OR")OR", S'R"R"A', and N\*R9R11R12A-, groups selected from the group consisting of alkyl, oxo, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, SR<sup>13</sup>, S(O)R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, SO<sub>3</sub>R<sup>13</sup>, wherein quaternary heterocycle and quaternary NR<sup>13</sup>OR<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, NO<sub>2</sub>, CO<sub>2</sub>R<sup>13</sup>, CN, OM, SO<sub>2</sub>OM,  ${
m So_2}{
m NR}^{13}{
m R}^{14}$ ,  ${
m C(0)}{
m NR}^{13}{
m R}^{14}$ ,  ${
m C(0)}{
m OM}$ ,  ${
m COR}^{13}$ ,  ${
m P(0)}{
m R}^{13}{
m R}^{14}$ alkenyl, alkynyl, polyalkyl, polyether, aryl,

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OH, or SH and when  $\mathbb{R}^5$  is OH,  $\mathbb{R}^1$ ,  $\mathbb{R}^2$ ,  $\mathbb{R}^3$ ,  $\mathbb{R}^4$ ,  $\mathbb{R}^7$  and  $\mathbb{R}^8$ provided that both  $R^5$  and  $R^6$  cannot be hydrogen,

provided that when R' or R' is phenyl, only one of cannot be all hydrogen;

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anilido, or anilinocarbonyl, only one of R' or R' is provided that when q = 1 and R\* is styryl,

A compound of claim 1, wherein  ${\rm R}^5$  and  ${\rm R}^6$  are independently selected from the group consisting of H,

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quaternary heteroaryl, aryl, heterocycle, quaternary heterocycle, and

 $P^{+}R^{13}R^{14}R15A-$ , P(OR'')OR'', S+R''R''A-, and  $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  ${\rm NR}^{13}{\rm OR}^{14}$ ,  ${\rm NR}^{13}{\rm NR}^{14}{\rm R}^{15}$ ,  ${\rm NO}_2$ ,  ${\rm CO}_2{\rm R}^{13}$ ,  ${\rm CN}$ ,  ${\rm OM}$ ,  ${\rm SO}_2{\rm OM}$ , oxo,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(0)R^{13}$ ,  $SO_2R^{13}$ ,  $SO_3R^{13}$ , P\*R<sup>7</sup>R<sup>8</sup>A-, or phenylene, NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7, P(0)R7, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, can optionally have one or more carbons replaced by 0, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle  $SO_2NR^{13}R^{14}$ , C(0)NR<sup>13</sup>R<sup>14</sup>, C(0)OM, COR<sup>13</sup>, P(0)R<sup>13</sup>R<sup>14</sup> independently selected from the group consisting of substituted with one or more substituent groups heterocycle, and quaternary heteroaryl can be wherein said alkyl, alkenyl, alkynyl, polyalkyl, wherein said aryl, heteroaryl, quaternary

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 $conr^7 r^8$ ,  $n^+ r^7 r^8 r^9 a^-$ , alkyl, alkenyl, alkynyl, aryl,  $NR^{7}R^{8}$ ,  $SR^{7}$ ,  $S(0)R^{7}$ ,  $SO_{2}R^{7}$ ,  $SO_{3}R^{7}$ ,  $CO_{2}R^{7}$ , CN, OXO, heterocycle, quaternary heteroaryl, P(0)R7R8, P+R7R8cycloalkyl, heterocycle, arylalkyl, quaternary groups selected from the group consisting of OR', can be further substituted with one or more substituent polyether, aryl, haloalkyl, cycloalkyl, and heterocycle and P(O)(OR')OR'. wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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the formula A compound of claim 2, wherein R' or R' has

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-Ar-(R'),

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wherein:

t is an integer from 0 to 5;

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benzoxazolyl, benzothiazolyl, and benzoisothiazolyl; triazolyl, isothiazolyl, indolyl, benzoimidazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, Ar is selected from the group consisting of

 $SR^9$ ,  $S(0)R^9$ ,  $SO_2R^9$ , and  $SO_3R^9$ cycloalkyl, heterocycle, quaternary heterocycle, OR9, group consisting of H, alkyl, alkenyl, alkynyl, aryl, one or more  $R^{\mathbf{Y}}$  are independently selected from the

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N+R9R11R12A-,  $P(0)R^{13}R^{14}$ ,  $P^{\dagger}R^{13}R^{14}R15A$ -,  $P(OR^{11})OR^{14}$ ,  $S^{\dagger}R^{11}R^{14}$ , and OM, SO20M, SO2NR $^{13}$ R $^{14}$ , C(O)NR $^{13}$ R $^{14}$ , C(O)OM, COR $^{13}$ , arylalkyl, halogen, oxo,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(O)R^{13}$ polyether, aryl, haloalkyl, cycloalkyl, heterocycle,  ${\rm SO_2R^{13}}$ ,  ${\rm SO_3R^{13}}$ ,  ${\rm NR^{13}OR^{14}}$ ,  ${\rm NR^{13}NR^{14}R^{15}}$ ,  ${\rm NO_2}$ ,  ${\rm CO_2R^{13}}$ ,  ${\rm CN_2}$ group consisting of alkyl, alkenyl, alkynyl, polyalkyl, and heterocycle can be substituted with one or more substituent groups independently selected from the wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

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heterocycle, quaternary heteroaryl, P(0)R<sup>7</sup>R<sup>8</sup>, P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A  $CONR^{7}R^{8}$ ,  $N^{+}R^{7}R^{8}R^{9}A^{-}$ , alkyl, alkenyl, alkynyl, aryl,  $NR^{7}R^{8}$ ,  $SR^{7}$ ,  $S(0)R^{7}$ ,  $SO_{2}R^{7}$ ,  $SO_{3}R^{7}$ ,  $CO_{2}R^{7}$ , CN,  $OXO_{1}$ groups selected from the group consisting of OR cycloalkyl, heterocycle, arylalkyl, quaternary can be further substituted with one or more substituent polyether, aryl, haloalkyl, cycloalkyl, and heterocycle and P(O)(OR')OR', and wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, wherein said alkyl, alkenyl, alkynyl, polyalkyl,

NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7, P(O)R',

P+R7R8A-, or phenylene.

4. A compound of claim 3, wherein R<sup>5</sup> or R<sup>6</sup> has the formula (II)



(II)

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A compound of claim 4, wherein n is 1 or 2. <u>ي</u>

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ö A compound of claim 5, wherein one of  $\mathbb{R}^7$  $R^8$  is H and the other of R' or R' is alkyl. A compound of claim 5, wherein both  $\mathbf{R}^7$  and  $\mathbf{R}^8$ are H.

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A compound of claim 7, wherein R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of H and alkyl. 9. A compound of claim 8, wherein said alkyl is

C1-C10 alkyl.

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10. A compound of claim 8, wherein R' and R' are both alkyl. 11. A compound of claim 10, wherein said alkyl is a C1-C10 alkyl.

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12. A compound of claim 11, wherein said alkyl is

a C,-C, alkyl.

13. A compound of claim 12, wherein said alkyl is

a C,-C, alkyl.

S

14. A compound of claim 13, wherein said alkyl is independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

15. A compound of claim 8, wherein R' and R' are each n-butyl. 16. A compound of claim 8, wherein one of R1 and

R2 is ethyl and the other of R' and R' is n-butyl.

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ò 17. A compound of claim 15, wherein q is 1, 2, ä

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or 18. A compound of claim 16, wherein q is 1, 2,

19. A compound of claim 17, wherein q is 1 or 2.

A compound of claim 19, wherein q is 1. 20.

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A compound of claim 18, wherein q is 1 or 2. 21.

A compound of claim 21, wherein q is 1. 22.

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23. A compound of claim 19, wherein R' and R' are independently selected from the group consisting of H and OR'. 24. A compound of claim 21, wherein R' and R' are independently selected from the group consisting of H and OR'.

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25. A compound of claim 23, wherein R' is H.

26. A compound of claim 24, wherein R' is H.

 $R^{X}$  are in the 7-, 8-, or 9-position of the benzo ring of formula (I). 27. A compound of claim 25, wherein one or more

the 7-, 8-, or 9- position of the benzo ring of formula Ĥ. A compound of claim 26, wherein said R is in

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Ξ). in the 7- and 9- positions of the benzo ring of formula A compound of claim 27, wherein said R" are

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the 7-position of the benzo ring of formula (I) 30. A compound of claim 28, wherein said  $R^X$  is in

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more  $R^{\mathbf{X}}$  are independently selected from the group NR"C(0)R", and NR"C(0)R", NR13NR14R15, N+R9R11R12A-, SR13, S+R13R14, CO2R13 polyalkyl, acyloxy, polyether, halogen, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup> consisting of alkyl, aryl, cycloalkyl, heterocycle, 31. A compound of claim 29, wherein said one or

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S(O)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, SO<sub>3</sub>R<sup>9</sup>, oxo, CO<sub>2</sub>R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup> polyalkyl, acyloxy, and polyether, can be further C(0)0M, and SO,OM, SO,NR'R", PO(OR")OR", P+R9R11R12A-, S'R'R"A-, or substituted with OR $^9$ , NR $^9$ R $^{10}$ , N $^+$ R $^9$ R $^{11}$ R $^{12}$ A $^-$ , SR $^9$ wherein alkyl, aryl, cycloalkyl, heterocycle,

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replaced by 0,  $NR^{13}$ ,  $N^{+}R^{13}R^{14}A^{-}$ , S, S0, S02,  $S^{+}R^{13}A^{-}$ ,  $^{3}$ , P(0)R", P $^{+}$ R $^{13}$ R $^{14}$ A-, phenylene, amino acid wherein in RX, one or more carbons are optionally

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polyalkyl, and peptide, polypeptide, carbohydrate, polyether, or

s, so, so<sub>2</sub>, s<sup>+</sup>R<sup>9</sup>A-, PR<sup>9</sup>, p<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, or P(0)R<sup>\*</sup> carbons are optionally replaced by 0, NR<sup>9</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, peptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid

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 $SR^{13}$ ,  $S_R^{+13}R^{14}$ ,  $CO_2R^{13}$ ,  $NR^{10}C(0)R^{13}$ , and  $NR^{10}C(0)R^{13}$ . halogen, OR13, NR13R14, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, selected from the group consisting of alkyl, aryl, 32. A compound of claim 30, wherein said  $R^{X}$  is , NR13NR14R15, N+R9R11R12A-,

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C(O)OM, and SO,OM, SO,NR'R", PO(OR")OR", P+R9R11R12A-, S'R'R"A-, or  $S(0)R^9$ ,  $SO_2R^9$ ,  $SO_3R^9$ , oxo,  $CO_2R^9$ , CN, halogen,  $CONR^9R^{10}$ polyalkyl, acyloxy, and polyether, can be further substituted with OR $^9$ , NR $^9$ R $^{10}$ , N $^+$ R $^9$ R $^{11}$ R $^{12}$ A $^-$ , SR $^9$ wherein alkyl, aryl, cycloalkyl, heterocycle

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peptide, polypeptide, carbohydrate, polyether, or  $pR^{13}$ ,  $P(0)R^{11}$ ,  $P^{\dagger}R^{13}R^{14}A^{-}$ , phenylene, amino acid, polyalkyl, and replaced by 0, NR  $^{13}$ , N  $^{\dagger}$ R  $^{13}$ R  $^{14}$ A-, S, SO, SO2, S  $^{\dagger}$ R  $^{13}$ A-, wherein in RX, one or more carbons are optionally

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s, so, so<sub>2</sub>, s<sup>+</sup>R<sup>9</sup>A-, PR<sup>9</sup>, P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, or P(0)R' peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR $^9$ , N $^+$ R $^9$ R $^{10}$ Awherein in said polyalkyl, phenylene, amino acid,

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more Rx are independently selected from the group consisting of polyether, OR", NR"R", and N+R9R11R12A-A compound of claim 31, wherein said one or

34. A compound of the claim 32, wherein said Rx is selected from the group consisting of polyether, OR", NR"R", and N+R $^9$ R $^1$ R $^1$ 2A $^-$ .

35. A compound of claim 33, wherein said one or more Rx are independently selected from the group consisting of  $OR^{11}$  and  $NR^{11}R^{11}$ .

36. A compound of claim 34, wherein said R' is independently selected from the group consisting of OR" and NR"R".

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37. A compound of claim 35, wherein  $R^{11}$  and  $R^{44}$  each methyl.

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38. A compound of the claim 36, wherein  $R^{11}$  and  $R^{14}$  each methyl.

39. A compound of claim 31, wherein one or more  $R^{y}$  are independently in the 3- or the 4-position of the phenyl ring of formula (II).

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40. A compound of claim 32, wherein one or more Ry are independently in the 3- or the 4- position of the phenyl ring of formula (II).

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41. A compound of claim 39, wherein t is 1 or 2.

42. A compound of claim 40, wherein t is 1 or 2.

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43. A compound of claim 41, wherein said one or more  $R^{y}$  are independently selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, NR<sup>13</sup>R<sup>14</sup>, NR'C(0)R'', and OR'',

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wherein alkyl and polyether can be further substituted with  ${\rm So_3R^9}$ ,  ${\rm N^+R^9R^{11}R^{12}A^-}$ , and quaternary heteroaryl.

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44. A compound of claim 42, wherein said  $R^y$  is independently selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, NR $^{13}R^{14}$ , NR $^{16}(0)R^{13}$ , and OR $^{13}$ ,

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wherein alkyl and polyether can be further substituted with  ${\rm SO_3R^9}$ ,  ${\rm N^+R^9R^{11}R^{12}A^-}$ , and quaternary heteroaryl.

45. A compound of claim 43, wherein said one or more  $R^Y$  are independently selected from the group consisting of alkyl, polyether, fluoride,  $NR^{13}R^{14}$ ,  $NR^{15}(O)R^{11}$ , and  $OR^{11}$ ,

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wherein alkyl and polyether can be further substituted with  ${\rm SO_3R^9},~{\rm N^4R^9R^{11}R^{12}A^-},~{\rm and~quaternary}$  heteroaryl.

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46. A compound of claim 44 wherein said  $R^Y$  is independently selected from the group consisting of alkyl, polyether, fluoride,  $NR^{13}R^{14}$ ,  $NR^{12}C(0)R^{11}$ , and  $OR^{11}$ ,

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wherein alkyl and polyether can be further substituted with  ${\rm SO3R}^9$ ,  ${\rm N}^+{\rm R}^9{\rm R}^{11}{\rm R}^{12}{\rm A}^-$ , and quaternary heteroaryl.

47. A compound of claim 45, wherein said  $R^{\prime\prime}$  and  $R^{\prime\prime}$  are alkyl,

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wherein alkyl can be further substituted with SO'R',  $N^+R^9R^{11}R^{12}A^-$ , and quaternary heteroaryl.

48. A compound of claim 46, wherein said  $R^{\iota}$  and  $R^{\iota \nu}$  are alkyl,

wherein alkyl can be further substituted with SO'R', N $^{+}R^{9}R^{11}R^{12}A^{-}$  , and quaternary heteroaryl.

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49. A compound of claim 47, wherein n is 2.

50. A compound of claim 48, wherein n is 2.

is in a syn relationship to said structure of formula (II). 51. A compound of claim 49, wherein said OH group

(II). is in a sym relationship to said structure of formula 52. A compound of claim 50, wherein said OH group

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53. A compound of claim 51, having the formula:

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54. A compound of claim 51, having the formula:

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오" N(CH2CH3)3 [A-]

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55. A compound of claim 51, having the formula:

56. A compound of claim 51, having the formula:

57. A compound of claim 51, having the formula:

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OH (A-1)

58. A compound of claim 52, having the formula:

59. A compound of claim 52, having the formula:

60. A compound of claim 52, having the formula:

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오"

중,

N(CH2CH3)3

[A-]

61. A compound of claim 52, having the formula:

62. A compound of claim 52, having the formula:

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- 63. A compound of claim 31, wherein n is 1.
- 64. A compound of claim 63, wherein R' is H.
- 65. A compound of claim 64, having the formula

- and alkyl. independently selected from the group consisting of H 66. A compound of claim 4, wherein R' and R' are
- C<sub>1</sub>-C<sub>10</sub> alkyl. 67. A compound of claim 66, wherein said alkyl is

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C,-C, alkyl. 68. A compound of claim 67, wherein said alkyl is

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69. A compound of claim 68, wherein said alkyl is C,-C, alkyl.

- 70. A compound of claim 69, wherein R' and R' are independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.
- 71. A compound of claim 4, wherein R' and R' are independently selected from the group consisting of H and OR'.

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- 72. A compound of claim 71, wherein R' is H.
- 73. A compound of claim 4, wherein n is 2.

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- 74. A compound of claim 3, wherein R' and R' are independently selected from the group consisting of H and OR'.
- 75. A compound of claim 74, wherein R<sup>9</sup> is H.

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- 76. A compound of claim 3, wherein one of  $\mathbb{R}^7$  or  $\mathbb{R}^8$  is H.
- 77. A compound of claim 76, wherein both R' and R' are H.

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78. A compound of claim 3, wherein said one or more R<sup>X</sup> are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, NR<sup>13</sup>R<sup>14</sup>, CO<sub>2</sub>R<sup>13</sup>, NR<sup>13</sup>RR<sup>14</sup>, CO<sub>2</sub>R<sup>13</sup>, NR<sup>13</sup>C(O)R<sup>13</sup>, and NR<sup>13</sup>C(O)R<sup>13</sup>,

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wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>9</sup>,

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 $S(0)R^9$ ,  $SO_2R^9$ ,  $SO_3R^9$ , oxo,  $CO_2R^9$ , CN, halogen,  $CONR^9R^{10}SO_4OM$ ,  $SO_4NR^3R^{10}$ ,  $PO(OR^{16})OR^{17}$ ,  $P^+R^9R^{11}R^{12}A^-$ ,  $S^-R^8R^{10}A^-$ , or C(O)OM, and

wherein in  $R^{X}$ , one or more carbons are optionally replaced by 0,  $NR^{13}$ ,  $N^{+}R^{13}R^{14}A^{-}$ , S, S0, S0<sub>2</sub>,  $S^{+}R^{13}A^{-}$ ,  $PR^{13}$ ,  $P(0)R^{13}$ ,  $P^{+}R^{13}R^{14}A$ , phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR<sup>9</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>9</sup>A<sup>-</sup>, PR<sup>9</sup>, P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>, or P(O)R<sup>+</sup>.

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79. A compound of claim 78, wherein said one or more R are independently selected from the group consisting of polyether, OR", NR"R", and N\*R9R11R12A-.

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80. A compound of claim 79, wherein said one or more R' are independently selected from the group consisting of OR" and NR"R".

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- 81. A compound of claim 80, wherein  $R^{13}$  and  $R^{14}$  are each methyl.
- 82. A compound of claim 3, wherein one or more  $\mathbb{R}^{Y}$  are independently in the 3- or the 4-position of the phenyl ring of formula (II).

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83. A compound of claim 82, wherein one or more  $R^{\rm y}$  is selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide,  ${\rm NR}^9 R^{10}$ , and  ${\rm NC}(0) R^9$ ,

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wherein alkyl and polyether can be substituted with  ${\rm SO}_3{\rm R}^9,~{\rm N}^4{\rm R}^9{\rm R}^{11}{\rm R}^{12}{\rm A}^{-},$  and quaternary heteroaryl.

are alkyl. 84. A compound of claim 83, wherein  $^9$  and  $^{10}$ 

 $\mathbf{R}^{\mathbf{Y}}$  is selected from the group consisting of alkyl and NC(0)R9 polyether, fluoride, chloride, bromide, iodide,  $NR^9R^{10}$ 85. A compound of claim 84, wherein one or more

polyalkyl, acyloxy, polyether, halogen,  $OR^{13}$ ,  $NR^{13}R^{14}$ NR"C(0)R", and NR"C(0)R", NR13NR14R15, N+R9R11R12A-, SR13, S+R13R14, CO2R13 consisting of alkyl, aryl, cycloalkyl, heterocycle, more  $R^{\mathbf{X}}$  are independently selected from the group 86. A compound of claim 1, wherein said one or

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C(O)OM, and SO,OM, SO,NR'R", PO(OR")OR", P\*R9R11R12A-, S'R'R"A, or S(O)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, SO<sub>3</sub>R<sup>9</sup>, oxo, CO<sub>2</sub>R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup> substituted with OR $^9$ , NR $^9$ R $^{10}$ , N $^+$ R $^9$ R $^{11}$ R $^{12}$ A $^-$ , SR $^9$ polyalkyl, acyloxy, and polyether, can be further wherein alkyl, aryl, cycloalkyl, heterocycle,

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peptide, polypeptide, carbohydrate, polyether, or  $pR^{13}$ ,  $p(0)R^{11}$ ,  $p^{+}R^{13}R^{14}A^{-}$ , phenylene, amino acid, replaced by 0,  $NR^{13}$ ,  $N^{+}R^{13}R^{14}A^{-}$ , s, so, so<sub>2</sub>,  $S^{+}R^{13}A^{-}$ , polyalkyl, and wherein in RX, one or more carbons are optionally

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carbons are optionally replaced by 0, NR<sup>9</sup>, N<sup>†</sup>R<sup>9</sup>R<sup>10</sup>Apeptide, polypeptide, and carbohydrate, one or more SO, SO2, S+R9A-, PR9, P+R9R10A-, or P(0)R' wherein in said polyalkyl, phenylene, amino acid

87. A compound of claim 1, wherein n is 1 or 2.

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- 88. A compound of claim 87, wherein n is 2.
- and alkyl. independently selected from the group consisting of H 89. A compound of claim 1, wherein R' and R' are

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- C,-C, alkyl. 90. A compound of claim 89, wherein said alkyl is
- C,-C, alkyl. 91. A compound of claim 90, wherein said alkyl is

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C,-C, alkyl. 92. A compound of claim 91, wherein said alkyl is

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- ethyl, n-propyl, n-butyl, and isobutyl. independently selected from the group consisting of 93. A compound of claim 92, wherein R' and R' are
- and OR'. independently selected from the group consisting of H 94. A compound of claim 1, wherein R and R are

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95. A compound of claim 94, wherein R' is H.

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- R<sup>8</sup> is H. A compound of claim 1, wherein one of  $R^7$  or
- are H. 97. A compound of claim 96, wherein both R' and R'

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A compound of the formula (III)

R<sup>8</sup> R<sup>1</sup> R<sup>2</sup> R<sup>19</sup> R<sup>19</sup> R<sup>19</sup> R<sup>19</sup> R<sup>10</sup> R<sup>1</sup>

S

wherein :

q and r are independently integers from 0 to 4; d and e are independently integers from 0 to 2; t and u are independently integers from 0 to 4; R', R', and R' are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

2

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of OR<sup>9</sup>, NR<sup>9</sup>R1<sup>0</sup>, N'R'R"RMA', SR<sup>9</sup>, S'R'A-. P'R'R"R"A', S(O)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, SO<sub>3</sub>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, CO<sub>3</sub>R<sup>9</sup>, CO

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wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR, N\*R'R<sup>10</sup>A-, S, SO, SO<sub>2</sub>, S\*R<sup>9</sup>A-, P\*R<sup>9</sup>R<sup>10</sup>A-, or phenylene,

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wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>w</sup> are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, and arylalkyl; or

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R' and R' taken together with the carbon to which they are attached form C,-C, cycloalkylidene, or R<sup>M</sup> and R<sup>M</sup> taken together with the carbon to which they are attached form C,-C, cycloalkylidene;

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R¹, R¹, R¹, and R⁴ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR³, NR³R¹0, SR³, S(O)R³, SO2R³, and SO3R³, wherein R¹ and R⁴ are as defined above; or

 $\rm R^3$  and  $\rm R^4$  together form =0, =NOR  $^{11}$ , =S, =NNR  $^{11}\rm R^{12}$ , or =CR  $^{11}\rm R^{12}$ , or  $\rm R^{3A}$  and  $\rm R^{4A}$  together form =0, =NOR  $^{11}$ , =S,

= $nnR^{11}R^{12}$ , = $nR^{9}$ , or = $cR^{11}R^{12}$ , wherein  $R^{11}$  and  $R^{12}$  are independently selected from the group consisting of H, alkyl, alkenyl, alvoyl, arvletkyl alkonylatvi, arvletkyl alkonylatvi, arvletkyl

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alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, SR<sup>9</sup>, S(0)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, SO<sub>3</sub>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, CN, halogen, oxo, and CONR<sup>9</sup>R<sup>10</sup>, wherein R<sup>9</sup> and R<sup>10</sup> are as defined above, provided that both R<sup>3</sup> and R<sup>4</sup> cannot be OH, NH2, and SH, or

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 $\rm R^{11}$  and  $\rm R^{12}$  together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

wherein A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation;  $R^7,\ R^8,\ \text{and}\ R^4 \text{ are independently selected from}$ 

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the group consisting of hydrogen and alkyl; and one or more R<sup>X</sup> and R<sup>M</sup> are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle,

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polyether, quaternary heterocycle, quaternary

heteroaryl, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, SR<sup>13</sup>, S(O)R<sup>13</sup>, S(O)<sub>2</sub>R<sup>13</sup>,
SO<sub>3</sub>R<sup>13</sup>, S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A-, NR<sup>13</sup>OR<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, NO<sub>2</sub>, CO<sub>2</sub>R<sup>13</sup>,
CN, OM, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, NR''C(O)R", C(O)NR<sup>13</sup>R<sup>14</sup>,
NR14C(O)R13, C(O)OM, COR<sup>13</sup>, OR<sup>18</sup>, S(O)<sub>D</sub>NR<sup>18</sup>, NR<sup>13</sup>R<sup>18</sup>,

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×

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peptide, polypeptide, and carbohydrate, NR 18 OR 14, N+R 9R 11R 12A-, P+R 9R 11R 12A-, amino acid.

 $p^+R^9R^{11}R^{12}A^-$ , S'R'R'A', or C(0)0M, and CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, PO(OR<sup>11</sup>)OR<sup>11</sup>  $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  $SR^{9}$ ,  $S(0)R^{9}$ ,  $S0_{2}R^{9}$ ,  $S0_{3}R^{9}$ ,  $O(0)R^{9}$ heteroaryl can be further substituted with  $OR^9$ ,  $NR^9R^{10}$ polyether, quaternary heterocycle, and quaternary polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl, wherein  $R^{18}$  is selected from the group consisting

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with one or more substituent selected from the group  $SO_2OM$ ,  $SO_2NR^9R^{10}$ ,  $PO(OR^{16})OR^{17}$ , and C(O)OM, SO2R9, SO3R9, oxo, CO2R9, CN, halogen, CONR9R10, SO3R9 consisting of  $OR^9$ ,  $NR^9R^{10}$ ,  $N^+R^9R^{11}R^{12}A^-$ ,  $SR^9$ ,  $S(0)R^9$ and quaternary heteroaryl optionally are substituted heterocycle, heterocycle, alkyl quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl

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 $S^{+}R^{13}A-$ ,  $PR^{13}$ , P(O)R13,  $P^{+}R^{13}R^{14}A-$ , phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or optionally replaced by O,  $NR^{13}$ ,  $N^{\dagger}R^{13}R^{14}A^{-}$ , S, SO, SO<sub>2</sub>, polyalkyl, wherein in  $R^*$  and  $R^*$ , one or more carbons are

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s, so, so2, s+R9A-, PR9, P+R9R10A-, or P(0)R'; carbons are optionally replaced by 0, NR $^9$ , N $^{\dagger}$ R $^{10}$ Apeptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid

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alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more wherein quaternary heterocycle and quaternary

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P+R<sup>13</sup>R<sup>14</sup>R15A-, P(OR")OR", S'R"R"A, and N+R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A-,  $SO_2NR^{13}R^{14}$ ,  $C(0)NR^{13}R^{14}$ , C(0)OM,  $COR^{13}$ ,  $P(0)R^{13}R^{14}$  ${
m NR}^{13}{
m OR}^{14}$ ,  ${
m NR}^{13}{
m NR}^{14}{
m K}^{15}$ , NO2, CO2R<sup>13</sup>, CN, OM, SO2OM, oxo,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(O)R^{13}$ ,  $SO_{2}R^{13}$ ,  $SO_{3}R^{13}$ ,

quatarmary heterocycle, quaternary heteroaryl, or aryl, SO, SÓ2, S+R7R8, PR7, P+R7R8, phenylene, heterocycle, have one or more carbon replaced by O, NR7, N+R7R8, S, diyl, polyether diyl, polyalkoxy diyl, carbohydrate, diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy R" is selected from the group consisting of alkane

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 $N^{+}R^{9}R^{11}R^{12}A^{-}$ ;  $P(0)R^{13}R^{14}$ ,  $P^{\dagger}R^{13}R^{14}R15A$ -,  $P(0R^{11})OR^{14}$ ,  $S^{\prime}R^{14}R^{14}A^{\prime}$ , and ом, so<sub>2</sub>om, so<sub>2</sub> $NR^{13}R^{14}$ , c(o) $NR^{13}R^{14}$ , c(o)om, co $R^{13}$  $SO_2R^{13}$ ,  $SO_3R^{13}$ ,  $NR^{13}OR^{14}$ ,  $NR^{13}NR^{14}R^{15}$ ,  $NO_2$ ,  $CO_2R^{13}$ , CN, arylalkyl, halogen, oxo, OR $^{13}$ , NR $^{13}$ R $^{14}$ , SR $^{13}$ , S(O)R $^{13}$ polyether, aryl, haloalkyl, cycloalkyl, heterocycle, group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and substituent groups independently selected from the polypeptide can be substituted with one or more polyalkane diyl, alkoxy diyl, polyether diyl, wherein alkane diyl, alkene diyl, alkyne diyl,

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quaternary heterocycle,  $OR^9$ ,  $SR^9$ ,  $S(O)R^9$ ,  $SO_2R^9$ , and alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, selected from from the group consisting of H, alkyl, wherein one or more R' and R" are independently

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and heterocycle can be substituted with one or more substituent groups independently selected from the wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

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group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, SR<sup>13</sup>, S(O)R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, SO<sub>3</sub>R<sup>13</sup>, NR<sup>13</sup>OR<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, NO<sub>2</sub>, CO<sub>2</sub>R<sup>13</sup>, OM, SO<sub>2</sub>OM, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, C(O)NR<sup>13</sup>R<sup>14</sup>, C(O)OM, COR<sup>13</sup>, P(O)R<sup>13</sup>R<sup>14</sup>, p<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R1SA-, P(OR<sup>1</sup>)OR<sup>1</sup>, S'R''R'A, and N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR<sup>7</sup>, NR<sup>7</sup>R<sup>8</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO2R<sup>7</sup>, CO2R<sup>7</sup>, CN, OXO, CONR<sup>7</sup>R<sup>8</sup>, N\*R<sup>8</sup>R<sup>8</sup>A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heterocycle, quaternary heterocycle, and

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR $^7$ , N $^4$ R $^8$ A-, S, SO, SO $_2$ , S $^4$ R $^7$ A-, PR $^7$ , P(O)R $^7$ , P $^7$ R $^8$ A-, or phenylene.

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99. A compound of claim 98, wherein  $R^{i}$ ,  $R^{u}$ ,  $R^{i}$ , and  $R^{u}$  are independently selected from the group consisting of H and alkyl.

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100. A compound of claim 99, wherein R¹, R¹, and R³ are independently selected from the group consisting of H and C₁-C₁ alkyl.

101. A compound of claim 100, wherein said alkylis a C,-C, alkyl.

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102. A compound of claim 101, wherein  $R^1$ ,  $R^{\mu}$ ,  $R^2$ , and  $R^{\mu}$  are independently  $C_1$ - $C_4$  alkyl.

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103. A compound of claim 102, wherein R', R", R', and R" are independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

104. A compound of claim 98, wherein R', R", R", and R" are independently selected from the group consisting of H and OR".

105. A compound of claim 104, wherein R' is H.

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106. A compound of claim 98, wherein R', R", R', and R" are H.

107. A compound of claim 98, wherein d and e are independently 1 or 2.

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108. A compound of claim 107, wherein d and e are both 2.

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109. A compound of claim 98, wherein one or more R<sup>X</sup> and one or more R<sup>M</sup> are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>13</sup>, S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>, CO<sub>2</sub>R<sup>13</sup>, NR''C(O)R'', and NR''C(O)R'',

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wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, N<sup>†</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>9</sup>, S(0)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, OxO, CO<sub>2</sub>R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup> SO<sub>2</sub>OM, SO<sub>4</sub>NR<sup>†</sup>R<sup>\*</sup>, PO(OR<sup>\*\*</sup>)OR<sup>\*\*</sup>, p<sup>†</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, S'R<sup>†</sup>R<sup>†\*</sup>A<sup>\*</sup>, or C(0)OM, and

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wherein in  $\rm R^X$ , one or more carbons are optionally replaced by 0,  $\rm NR^{13}, \, N^{+}R^{13}R^{14}A_{-}, \, S, \, S0, \, S0_2, \, S^{+}R^{13}A_{-},$   $\rm PR^{13}, \, P(0)R^{11}, \, P^{+}R^{13}R^{14}A_{-}, \, phenylene, \, amino \, acid,$ 

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peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

carbons are optionally replaced by O, NR<sup>9</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, peptide, polypeptide, and carbohydrate, one or more so, so<sub>2</sub>, s<sup>+</sup>R<sup>9</sup>A-, PR<sup>9</sup>, P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, or P(0)R\*. wherein in said polyalkyl, phenylene, amino acid

substituted with  ${\rm SO_{3}R^9},~{\rm N^{\dagger}R^9R^{11}R^{12}A^{-}},~{\rm and}~{\rm quaternary}$ the group consisting of alkyl, polyether, fluoride,  $R^{Y}$  and one or more  $R^{\prime\prime}$  are independently selected from heteroaryl. chloride, bromide, iodide, NR<sup>13</sup>R<sup>14</sup>, NR"C(0)R", and OR" wherein alkyl and polyether can be further 110. A compound of claim 98, wherein one or more

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have one or more carbon replaced by 0, NR7, N+R7R8, S, polyalkane diyl, alkoxy diyl, and polyalkoxy diyl, selected from the group consisting of alkane diyl, SO, SO2, S+R7R8, PR7, P+R7R8, or phenylene. wherein alkane diyl and polyalkane diyl can optionally 111. A compound of claim 98, wherein R" is

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 $S^{+}R^{0}R^{10}$ ,  $P^{+}R^{0}R^{10}$ , phenylene, amino acid, peptide optionally replaced by 0,  $NR^9$ ,  $N^+R^9R^{10}$ , S, S0, S02 selected from the group consisting of alkoxy diyl and polypeptide, carbohydrate, or polyalkyl. polyalkoxydiyl wherein one or more carbons are 112. A compound of claim 111, wherein R" is

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and  $R^{**}$  are independently selected from the group consisting of H and alkyl. 113. A compound of claim 112, wherein R', R', R'

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and  $R^{\omega}$  are independently selected from the group consisting of H and OR'. 114. A compound of claim 113, wherein R', R', R'

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115. A compound of claim 114, wherein R' is H.

and R" are each H. 116. A compound of claim 115, wherein R', R', R',

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independently 1 or 2. 117. A compound of claim 116, wherein d and e are

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polyalkyl, acyloxy, and polyether, can be further  $s^{+}R^{13}R^{14}$ ,  $CO_2R^{13}$ ,  $NR^{11}C(O)R^{13}$ , and  $NR^{11}C(O)R^{13}$ , OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>13</sup> heterocycle, polyalkyl, acyloxy, polyether, halogen the group consisting of alkyl, aryl, cycloalkyl,  $R^{\mathbf{X}}$  and one or more  $R^{\mathbf{M}}$  are independently selected from wherein alkyl, aryl, cycloalkyl, heterocycle 118. A compound of claim 117, wherein one or more

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SO,OM, SO,NR'R", PO(OR")OR", P+R9R11R12A-, S'R'R"A-, or S(0)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, SO<sub>3</sub>R<sup>9</sup>, oxo, CO<sub>2</sub>R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup> substituted with or  $^9$ , NR  $^9\mathrm{R}^{10}$ , N $^+\mathrm{R}^9\mathrm{R}^{11}\mathrm{R}^{12}\mathrm{A}^-$ , SR  $^9$ 

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peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and  $pR^{13}$ ,  $P(0)R^{11}$ ,  $p^{+}R^{13}R^{14}A^{-}$ , phenylene, amino acid, replaced by 0,  $NR^{13}$ ,  $N^{\dagger}R^{13}R^{14}A^{-}$ , S, SO, SO<sub>2</sub>,  $S^{\dagger}R^{13}A^{-}$ , 'wherein in  $R^{\mathbf{x}}$ , one or more carbons are optionally

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s, so, so<sub>2</sub>, s<sup>†</sup>R<sup>9</sup>A-, PR<sup>9</sup>, P<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A-, or P(O)R<sup>3</sup>. carbons are optionally replaced by 0, NR<sup>3</sup>, N<sup>†</sup>R<sup>3</sup>R<sup>10</sup>Apeptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid

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찟 and one or more  $R^{\prime\prime}$  are independently selected from 119. A compound of claim 118, wherein one or more

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the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide,  $NR^{13}R^{14}$ ,  $NR^{4}C(0)R^{47}$ , and  $OR^{47}$  wherein alkyl and polyether can be further substituted with  $SO_3R^9$ ,  $N^4R^9R^{11}R^{12}A^-$ , and quaternary heteroaryl.

120. A compound of claim 119, having the formula:

PEG = 3400 molecular weight polyethylene glycol polymer chain

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121. A compound of the formula (IV)

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wherein :

q and r are independently integers from 0 to 3; d and e are independently integers from 0 to 2; t and u are independently integers from 0 to 5; R', R", R", and R" are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

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wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, N'R'R"R"A', SR<sup>9</sup>, S'R'A-. F'R'R"R"A', S(O)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, SO<sub>3</sub>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, CN, halogen, oxo, and CONR<sup>9</sup>R<sup>10</sup>,

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wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR<sup>9</sup>, N<sup>†</sup>8<sup>†10</sup>A-, S. SO, SO<sub>2</sub>, S<sup>†</sup>R<sup>3</sup>A-, P<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A-, or phenylene,

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wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>W</sup> are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, anylemmoniumalkyl, and arylalkyl; or

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they are attached form C,-C, cycloalkylidene, R" and R" taken together with the carbon to which

above; or SO2R , and SO3R , wherein R and R are as defined acyloxy, aryl, heterocycle, OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, SR<sup>9</sup>, S(0)R<sup>9</sup> the group consisting of H, alkyl, alkenyl, alkynyl,  $R^1$ ,  $R^{\prime\prime}$ ,  $R^{\prime\prime}$ , and  $R^{\prime\prime\prime}$  are independently selected from

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=NR9, or =CR11R12, or  $m R^3$  and  $m R^4$  together form =0, =NOR $^{11}$ , =S, =NNR $^{11}
m R^{12}$ 

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=NNR 11R 12, =NR 9, or =CR 11R 12,  $\mathbb{R}^{3\lambda}$  and  $\mathbb{R}^{4\lambda}$  together form =0, =NOR  $^{11}$ , =S

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both  $R^3$  and  $R^4$  cannot be OH, NH2, and SH, or wherein  $R^9$  and  $R^{10}$  are as defined above, provided that SO2R9, SO3R9, CO2R9, CN, halogen, oxo, and CONR9R10 cycloalkyl, cyanoalkyl,  $oR^9$ ,  $NR^9R^{10}$ ,  $SR^9$ ,  $S(0)R^9$ heterocycle, carboxyalkyl, carboalkoxyalkyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, from the group consisting of H, alkyl, alkenyl, wherein  $R^{11}$  and  $R^{12}$  are independently selected

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atom to which they are attached form a cyclic ring;  $m R^{11}$  and  $m R^{12}$  together with the nitrogen or carbon

and M is a pharmaceutically acceptable cation; wherein A is a pharmaceutically acceptable anion

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the group consisting of hydrogen and alkyl; and  $\mathrm{R}^7$ ,  $\mathrm{R}^\mathrm{u}$ ,  $\mathrm{R}^\mathrm{g}$ , and  $\mathrm{R}^\mathrm{u}$  are independently selected from

polyether, quaternary heterocycle, quaternary haloalkyl, cycloalkyl, heterocycle, heterocycle, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, heteroaryl,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(O)R^{13}$ ,  $S(O)_2R^{13}$ from the group consisting of H, alkyl, alkenyl, one or more  $R^{X}$  and  $R^{m}$  are independently selected

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peptide, polypeptide, and carbohydrate,  $NR^{18}OR^{14}$ ,  $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  $P^{+}R^{9}R^{11}R^{12}A^{-}$ , amino acid, NR14C(0)R13, C(0)OM,  $COR^{13}$ ,  $OR^{18}$ ,  $S(0)_{nNR}^{18}$ ,  $NR^{13}R^{18}$ CN, OM, SO20M, SO2NR $^{13}$ R $^{14}$ , NR $^{14}$ C(0)R $^{13}$ , C(0)NR $^{13}$ R $^{14}$  $SO_3R^{13}$ ,  $S^*R^{13}R^{14}A^-$ ,  $NR^{13}OR^{14}$ ,  $NR^{13}NR^{14}R^{15}$ ,  $NO_2$ ,  $CO_2R^{13}$ 

 $p^+R^0R^{11}R^{12}A^-$ , S'R'R'A', or C(0)0M, and CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, PO(OR")OR"  $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  $SR^{9}$ ,  $S(0)R^{9}$ ,  $SO_{2}R^{9}$ ,  $SO_{3}R^{9}$ ,  $O_{3}R^{9}$ ,  $O_{2}R^{9}$ polyether, quaternary heterocycle, and quaternary polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, heteroaryl can be further substituted with OR9, NR9R10 wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

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of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl, wherein  ${ t R}^{18}$  is selected from the group consisting

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 $SO_2OM$ ,  $SO_2NR^9R^{10}$ ,  $PO(OR^{16})OR^{17}$ , and C(O)OM. SO2R<sup>9</sup>, SO3R<sup>9</sup>, oxo, CO2R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO3R<sup>9</sup> consisting of  $OR^9$ ,  $NR^9R^{10}$ ,  $N^+R^9R^{11}R^{12}A^-$ ,  $SR^9$ ,  $S(0)R^9$ with one or more substituent selected from the group and quaternary heteroaryl optionally are substituted heterocycle, heterocycle, alkyl quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl

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 $S^{+}R^{13}A^{-}$ ,  $PR^{13}$ , P(O)R13,  $P^{+}R^{13}R^{14}A^{-}$ , phenylene, amino polyalkyl, acid, peptide, polypeptide, carbohydrate, polyether, or optionally replaced by 0,  $NR^{13}$ ,  $N^{+}R^{13}R^{14}A^{-}$ , S, S0, S02 wherein in R and R", one or more carbons are

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carbons are optionally replaced by 0,  $NR^9$ ,  $N^+R^9R^{10}A$ peptide, polypeptide, and carbohydrate, one or more so, so2, s+R9A-, PR9, p+R9R10A-, or P(0)R'; wherein in said r lyalkyl, phenylene, amino acid

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heteroaryl are optionally substituted with one or more wherein quaternary heterocycle and quaternary

haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, groups selected from the group consisting of alkyl,  $\text{So_2NR}^{13}\text{R}^{14}$ , C(0)NR $^{13}\text{R}^{14}$ , C(0)OM,  $\text{COR}^{13}$ , P(0)R $^{13}\text{R}^{14}$  $\cos$  oxo,  $\cos^{13}$ ,  $\sin^{13}$ R<sup>14</sup>,  $\sin^{13}$ ,  $\sin^{13}$ ,  $\sin^{23}$ ,  $\cos^{13}$ ,  $\cos^{13}$ ,  ${
m NR}^{13}{
m OR}^{14}$ ,  ${
m NR}^{13}{
m NR}^{14}{
m R}^{15}$ ,  ${
m NO}_2$ ,  ${
m CO}_2{
m R}^{13}$ ,  ${
m CN}$ ,  ${
m OM}$ ,  ${
m SO}_2{
m OM}$ , alkenyl, alkynyl, polyalkyl, polyether, aryl,

P\*R13R14R15A-, P(OR")OR", S'R"R"A", and N\*R9R11R12A-

R" is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy quatarnary heterocycle, quaternary heteroaryl, or aryl, have one or more carbon replaced by 0, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, phenylene, heterocycle, amino acid, and peptide, polypeptide, wherein alkane diyl, polyether diyl, polyalkoxy diyl, carbohydrate, diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally

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polyalkoxy diyl, carbohydrate, amino acid, peptide, and group consisting of alkyl, alkenyl, alkynyl, polyalkyl,  ${
m So_2 R^{13}}$ ,  ${
m So_3 R^{13}}$ ,  ${
m NR^{13} OR^{14}}$ ,  ${
m NR^{13} NR^{14} R^{15}}$ ,  ${
m No_2}$ ,  ${
m Co_2 R^{13}}$ ,  ${
m CN}$ , arylalkyl, halogen, oxo,  $\mathrm{OR}^{13}$ ,  $\mathrm{NR}^{13}\mathrm{R}^{14}$ ,  $\mathrm{SR}^{13}$ ,  $\mathrm{S(0)R}^{13}$ polyether, aryl, haloalkyl, cycloalkyl, heterocycle, wherein alkane diyl, alkene diyl, alkyne diyl, substituent groups independently selected from the P(0)R<sup>13</sup>R<sup>14</sup>, P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R15A-, P(0R")OR", S'R"R"A', and om, so<sub>2</sub>om, so<sub>2</sub>nr<sup>13</sup>r<sup>14</sup>, c(0)nr<sup>13</sup>r<sup>14</sup>, c(0)om, cor<sup>13</sup>, polypeptide can be substituted with one or more polyalkane diyl, alkoxy diyl, polyether diyl, N+R9R11R12A-;

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polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent wherein said alkyl, alkenyl, alkynyl, polyalkyl,  $NR^7R^8$ ,  $SR^7$ ,  $S(O)R^7$ ,  $SO_2R^7$ ,  $SO_3R^7$ ,  $CO_2R^7$ , CN, OxO, groups selected from the group consisting of  $\mathtt{OR}^7$ 

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heterocycle, quaternary heteroaryl, P(0)R<sup>7</sup>R<sup>8</sup>, P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A<sup>-</sup>, CONR<sup>7</sup>R<sup>8</sup>, N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>R<sup>9</sup>A-, alkyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary and P(O) (OR') OR', and

polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, wherein said alkyl, alkenyl, alkynyl, polyalkyl, NR7, N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>7</sup>A-, PR<sup>7</sup>, P(O)R',

P\*R'R\*A-, or phenylene.

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122. A compound of claim 121, wherein R', R", R", and R<sup>2</sup> are independently selected from the group consisting of H and alkyl. 123. A compound of claim 122, wherein R', R", R', and R<sup>28</sup> are independently selected from the group consisting of H and C,-C, alkyl.

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124. A compound of claim 123, wherein said alkyl is a C,-C, alkyl.

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125. A compound of claim 124, wherein R', R", R' and R" are independently C,-C, alkyl.

consisting of ethyl, n-propyl, n-butyl, and isobutyl. 126. A compound of claim 125, wherein R', R", R', and R" are independently selected from the group

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127. A compound of claim 125, wherein R', R", R', and Rt are independently selected from the group consisting of H and OR'.

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128. A compound of claim 127, wherein R' is H.

129. A compound of claim 121, wherein R', R', R', and R" are H.

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independently 1 or 2. 130. A compound of claim 121, wherein d and e are

both 2. 131. A compound of claim 130, wherein d and e are

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 $S^{\dagger}R^{13}R^{14}$ ,  $CO_2R^{13}$ ,  $NR^{14}C(O)R^{11}$ , and  $NR^{14}C(O)R^{13}$ , OR13, NR13R14, NR13NR14R15, N+R9R11R12A-, SR13, heterocycle, polyalkyl, acyloxy, polyether, halogen, the group consisting of alkyl, aryl, cycloalkyl,  $R^{\mathbf{x}}$  and one or more  $R^{\mathbf{u}}$  are independently selected from 132. A compound of claim 121, wherein one or more

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C(0)OM, and SO,OM, SO,NR'R", PO(OR")OR", P+R9R11R12A-, S'R'R"A-, or  $S(0)R^9$ ,  $SO_2R^9$ ,  $SO_3R^9$ , oxo,  $CO_2R^9$ , CN, halogen,  $CONR^9R^{10}$ polyalkyl, acyloxy, and polyether, can be further substituted with  $oR^9$ ,  $NR^9R^{10}$ ,  $N^+R^9R^{11}R^{12}A^-$ ,  $SR^9$ wherein alkyl, aryl, cycloalkyl, heterocycle,

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 $pR^{13}$ ,  $P(0)R^{11}$ ,  $p^{\dagger}R^{13}R^{14}A^{-}$ , phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or replaced by 0,  $NR^{13}$ ,  $N^{+}R^{13}R^{14}A^{-}$ , S, S0,  $S0_2$ ,  $S^{+}R^{13}A^{-}$ , wherein in  $R^{\mathbf{X}}$ , one or more carbons are optionally

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s, so, carbons are optionally replaced by 0,  $NR^9$ ,  $N^+R^9R^{10}A^-$ , peptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid, SO2, S<sup>+</sup>R<sup>9</sup>A-, PR<sup>9</sup>, P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, or P(0)R<sup>\*</sup>

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chloride, bromide, iodide,  $NR^{13}R^{14}$ ,  $NR^{11}C(0)R^{10}$ , and  $OR^{11}$ the group consisting of alkyl, polyether, fluoride, and one or more R\* are independently selected from 133. A compound of claim 121, wherein one or more

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heteroaryl. substituted with  $SO_3R^9$ ,  $N^+R^9R^{11}R^{12}A^-$ , and quaternary wherein alkyl and polyether can be further

polyalkane diyl, alkoxy diyl, and polyalkoxy diyl, SO, SO2, S+R7R8, PR7, P+R7R8, or phenylene. wherein alkane diyl and polyalkane diyl can optionally have one or more carbon replaced by O, NR7, N+R7R8, S, selected from the group consisting of alkane diyl, 134. A compound of claim 121, wherein R" is

 $\mathrm{S^{+}R^{9}R^{10}}$  ,  $\mathrm{pR^{9}}$  ,  $\mathrm{p^{+}R^{9}R^{10}}$  , phenylene, amino acid, peptide selected from the group consisting of alkoxy diyl and polypeptide, carbohydrate, or polyalkyl. optionally replaced by 0,  $NR^9$ ,  $N^+R^9R^{10}$ , s, s0, s02, polyalkoxydiyl wherein one or more carbons are 135. A compound of claim 134, wherein Rivis

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and  $\mathbf{R}^{\mathbf{A}}$  are independently selected from the group consisting of H and alkyl. 136. A compound of claim 135, wherein R1, R1, R2,

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and R" are independently selected from the group consisting of H and OR' 137. A compound of claim 136, wherein R', R'', 双

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138. A compound of claim 137, wherein R' is H.

and R" are each H. 139. A compound of claim 138, wherein R', R', R'

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independently 1 or 2. 140. A compound of claim 139, wherein d and e are

141. A compound of claim 140, having the formula:

PEG = 3400 molecular weight polyethylene glycol polymer chain

142. A compound of formula (V)

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wherein :

q is an integer from 0 to 4;

r is an integer from 0 to 3;

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d and e are independently integers from 0 to 2;

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t is an integer from 0 to 4;

u is an integer from 0 to 5;

R¹, R¹, and R¹ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, NR'R"RWA, SR<sup>9</sup>, S'R'A-. P'R'R"R"A', S(O)R<sup>9</sup>, SO2R<sup>9</sup>, SO3R<sup>9</sup>, CO2R<sup>9</sup>, CN, halogen, oxo, and CONR<sup>9</sup>R<sup>10</sup>,

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wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR<sup>9</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>9</sup>A-, P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, or phenylene,

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wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>w</sup> are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; or R¹ and R² taken together with the carbon to which

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they are attached form C,-C, cycloalkylidene, or R, and R, taken together with the carbon to which they are attached form C,-C, cycloalkylidene; R, R, R, and R are independently selected from

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the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle,  $0R^9$ ,  $NR^9R^{10}$ ,  $SR^9$ ,  $SO_2R^9$ , and  $SO_3R^9$ , wherein R' and R' are as defined above; or

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 $\rm R^3$  and  $\rm R^4$  together form =0, =NOR  $^{11},$  =S, =NNR  $^{11}\rm R^{12},$  =NF9, or =CR  $^{11}\rm R^{12},$  or

=NNR<sup>11</sup>R<sup>12</sup>, =NR<sup>9</sup>, or -=CR<sup>11</sup>R<sup>12</sup>  ${\tt R}^{3{\tt A}}$  and  ${\tt R}^{4{\tt A}}$  together form =0, =NOR  $^{11}$ , =S

both  $R^3$  and  $R^4$  cannot be OH, NH2, and SH, or  $\mathrm{SO_2R}^9$ ,  $\mathrm{SO_3R}^9$ ,  $\mathrm{CO_2R}^9$ , CN, halogen, oxo, and  $\mathrm{CONR}^9\mathrm{R}^{10}$ cycloalkyl, cyanoalkyl,  $OR^9$ ,  $NR^9R^{10}$ ,  $SR^9$ ,  $S(0)R^9$ alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl wherein  $R^9$  and  $R^{10}$  are as defined above, provided that heterocycle, carboxyalkyl, carboalkoxyalkyl from the group consisting of H, alkyl, alkenyl, wherein  $R^{11}$  and  $R^{12}$  are independently selected

atom to which they are attached form a cyclic ring;  $^{
m R}^{
m 11}$  and  $^{
m R}^{
m 12}$  together with the nitrogen or carbon 10

and M is a pharmaceutically acceptable cation. wherein A is a pharmaceutically acceptable anion

the group consisting of hydrogen and alkyl; and  $R^7$ ,  $R^n$ ,  $R^8$ , and  $R^m$  are independently selected from

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peptide, polypeptide, and carbohydrate,  $NR^{18}OR^{14}$ ,  $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  $P^{+}R^{9}R^{11}R^{12}A^{-}$ , amino acid NR14C(0)R13, C(0)OM,  $COR^{13}$ ,  $OR^{18}$ ,  $S(0)_{D}NR^{18}$ ,  $NR^{13}R^{18}$ heteroaryl,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(O)R^{13}$ ,  $S(O)_2R^{13}$ haloalkyl, cycloalkyl, heterocycle, heterocycle, CN, OM, SO20M, SO2NR $^{13}$ R $^{14}$ , NR $^{4}$ C(0)R $^{13}$ , C(0)NR $^{13}$ R $^{14}$ SO3R13, S+R13R14A-, NR13OR14, NR13NR14R15, NO2, CO2R13, polyether, quaternary heterocycle, quaternary alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen from the group consisting of H, alkyl, alkenyl, one or more RX and RY are independently selected

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 $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  $SR^{9}$ ,  $S(0)R^{9}$ ,  $S0_{2}R^{9}$ ,  $S0_{3}R^{9}$ ,  $O(0)R^{9}$ heteroaryl can be further substituted with or  $^{9}$ , NR $^{9}$ R $^{10}$ polyether, quaternary heterocycle, and quaternary polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl

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 $p^+R^9R^{11}R^{12}A^-$ , S'R'R'A', or C(O)OM, and CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, PO(OR")OR"

heterocycle, alky1, of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, wherein R<sup>18</sup> is selected from the group consisting

5020M,  $502NR^9R^{10}$ ,  $90(0R^{16})0R^{17}$ , and C(0)0M. SO2R<sup>9</sup>, SO3R<sup>9</sup>, oxo, CO2R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup>, SO3R<sup>9</sup> consisting of  $OR^9$ ,  $NR^9R^{10}$ ,  $N^+R^9R^{11}R^{12}A^-$ ,  $SR^9$ ,  $S(0)R^9$ with one or more substituent selected from the group and quaternary heteroaryl optionally are substituted heterocycle, heterocycle, alkyl quaternary heterocycle wherein acyl, arylalkoxycarbonyl, arylalkyl

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 $S^{+}R^{13}A^{-}$ ,  $PR^{13}$ , P(0)R13,  $P^{+}R^{13}R^{14}A^{-}$ , phenylene, amino polyalkyl, optionally replaced by O, Nr $^{13}$ , N $^{+}$ R $^{13}$ R $^{14}$ A-, S, SO, SO $_2$ . acid, peptide, polypeptide, carbohydrate, polyether, or wherein in R' and R", one or more carbons are

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s, so, so<sub>2</sub>, s<sup>+</sup>R<sup>9</sup>A-, pR<sup>9</sup>, p<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-, or P(0)R<sup>9</sup>; carbons are optionally replaced by 0, NR9, N+R9R10Apeptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid

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 $P^{+}R^{13}R^{14}R^{15}A^{-}$ ,  $P(OR^{11})OR^{11}$ ,  $S^{*}R^{11}R^{14}$ , and  $N^{+}R^{9}R^{11}R^{12}A^{-}$ ,  ${\rm NR}^{13}{\rm OR}^{14}$ ,  ${\rm NR}^{13}{\rm NR}^{14}{\rm R}^{15}$ ,  ${\rm NO}_2$ ,  ${\rm CO}_2{\rm R}^{13}$ ,  ${\rm CN}$ ,  ${\rm OM}$ ,  ${\rm SO}_2{\rm OM}$ , oxo,  $OR^{13}$ ,  $NR^{13}R^{14}$ ,  $SR^{13}$ ,  $S(O)R^{13}$ ,  $SO_2R^{13}$ ,  $SO_3R^{13}$  $SO_2NR^{13}R^{14}$ ; C(0)NR<sup>13</sup>R<sup>14</sup>, C(0)OM, COR<sup>13</sup>, P(0)R<sup>13</sup>R<sup>14</sup> haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, heteroaryl are optionally substituted with one or more alkenyl, alkynyl, polyalkyl, polyether, aryl, groups selected from the group consisting of alkyl, wherein quaternary heterocycle and quaternary

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diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate R" is selected from the group consisting of alkane

amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by 0, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, phenylene, heterocycle, quatarnary heterocycle, quatarnary heterocycle, or aryl,

wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, oR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, SR<sup>13</sup>, S(O)R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, NR<sup>13</sup>OR<sup>14</sup>, NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, NO<sub>2</sub>, CO<sub>2</sub>R<sup>13</sup>, CN, OM, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, C(O)NR<sup>13</sup>R<sup>14</sup>, C(O)OM, COR<sup>13</sup>, P(O)R<sup>13</sup>R<sup>14</sup>, P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R1SA-, P(OR")OR", SR<sup>13</sup>R<sup>14</sup>, and N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>;

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wherein one or more R' and R" are independently selected from from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR<sup>9</sup>, SR<sup>9</sup>, S(O)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, and SO<sub>3</sub>R<sup>9</sup>,

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wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocycle can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, SR<sup>13</sup>, S(O)R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, NR<sup>13</sup>O<sub>2</sub>R<sup>13</sup>, CO<sub>2</sub>R<sup>13</sup>, CO<sub>2</sub>R<sup>13</sup>, CO<sub>2</sub>R<sup>13</sup>, CO<sub>3</sub>R<sup>13</sup>, CO<sub>3</sub>R<sup>13</sup>, CO<sub>3</sub>R<sup>13</sup>, CO<sub>3</sub>R<sup>13</sup>, CO<sub>3</sub>R<sup>13</sup>, CO<sub>3</sub>R<sup>13</sup>, CO<sub>3</sub>R<sup>13</sup>, CO<sub>3</sub>R<sup>13</sup>, Prantalkyl, heterocycle, CO<sub>3</sub>R<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, C(O)NR<sup>13</sup>R<sup>14</sup>, C(O)OR, COO<sup>13</sup>, P(O)R<sup>13</sup>R<sup>14</sup>, Prantalkyl, Prantalkyl, Prantalkyl, Prantalkyl, CO<sub>3</sub>R<sup>13</sup>, OR, SO<sub>3</sub>R<sup>13</sup>, Prantalkyl, Prantalkyl, Prantalkyl, Coo<sup>13</sup>, P(O)R<sup>13</sup>R<sup>14</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>, P(OR<sup>1</sup>)OR<sup>1</sup>, Sr<sup>1</sup>R<sup>18</sup>A, and

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR<sup>7</sup>, NR<sup>7</sup>R, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO2R<sup>7</sup>, SO3R<sup>7</sup>, CO2R<sup>7</sup>, CN, OXO, CONR<sup>7</sup>R<sup>8</sup>, N<sup>‡</sup>R<sup>8</sup>R<sup>9</sup>A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heterocycle, quaternary heterocycle, and

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR<sup>7</sup>, N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>7</sup>A-, PR<sup>7</sup>, P(O)R<sup>7</sup>,

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P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-, or phenylene.

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143. A compound of claim 142, wherein  $R^i$ ,  $R^{ii}$ , and  $R^{ii}$  are independently selected from the group consisting of H and alkyl.

144. A compound of claim 143, wherein R', R", R', and R" are independently selected from the group consisting of H and C<sub>1</sub>-C<sub>1</sub>, alkyl.

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145. A compound of claim 144, wherein said alkyl is a  $C_2$ -C, alkyl.

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146. A compound of claim 145, wherein  $R^1,\ R^2,\ R^2$  and  $R^2$  are independently  $C_1\text{-}C_4$  alkyl.

147. A compound of claim 146, wherein R', R", R', and R" are independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

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148. A compound of claim 142, wherein R', R", R', and R" are independently selected from the group consisting of H and OR'.

149. A compound of claim 148, wherein R' is H.

150. A compound of claim 142, wherein  $R^1$ ,  $R^{1s}$ ,  $R^{1s}$ , and  $R^{1s}$  are H.

151. A compound of claim 142, wherein d and e are independently 1 or 2.

152. A compound of claim 151, wherein d and e are both 2.

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153. A compound of claim 142, wherein one or more R<sup>X</sup> and one or more R<sup>\*</sup> are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, NR<sup>13</sup>R<sup>14</sup>R<sup>15</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>13</sup>, S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>, CO2R<sup>13</sup>, NR"C(O)R", and NR"C(O)R",

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wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR<sup>9</sup>, NR<sup>9</sup>R<sup>10</sup>, N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, SR<sup>9</sup>, S(0)R<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup>, SO<sub>3</sub>R<sup>9</sup>, oxo, CO<sub>2</sub>R<sup>9</sup>, CN, halogen, CONR<sup>9</sup>R<sup>10</sup> SO<sub>2</sub>OM, SO<sub>3</sub>NR<sup>3</sup>R<sup>10</sup>, PO(OR<sup>14</sup>)OR<sup>13</sup>, P<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>, S'R'R<sup>10</sup>A<sup>-</sup>, or C(O)OM, and

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wherein in  $R^x$ , one or more carbons are optionally replaced by 0,  $NR^{13}$ ,  $N^+R^{13}R^{14}A^-$ , S, SO,  $SO_2$ ,  $S^+R^{13}A^-$ ,  $PR^{13}$ ,  $P(0)R^{13}$ ,  $P^+R^{13}R^{14}A^-$ , phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

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wherein in said polyalkyl, phenylene, amino acid peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR $^9$ , N $^+$ R $^1$ O<sub>A-</sub>, s, so, so<sub>2</sub>, s $^+$ R $^9$ A-, pR $^9$ , p $^+$ R $^1$ O<sub>A-</sub>, or P(0)R $^1$ .

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154. A compound of claim 142, wherein one or more  $\mathbf{R}^{\mathbf{Y}}$  and one or more  $\mathbf{R}^{\mathbf{Y}}$  are independently selected from

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the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide,  $nR^{13}R^{14}$ ,  $nR^{12}C(0)R^{11}$ , and  $OR^{11}$  wherein alkyl and polyether can be further substituted with  $SO_3R^9$ ,  $N^+R^9R^{11}R^{12}A^-$ , and quaternary heteroaryl.

155. A compound of claim 142, wherein R" is selected from the group consisting of alkane diyl, polyalkane diyl, alkoxy diyl, and polyalkoxy diyl, wherein alkane diyl and polyalkane diyl can optionally have one or more carbon replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, or phenylene.

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- 156. A compound of claim 155, wherein R" is selected from the group consisting of alkoxy diyl and polyalkoxydiyl wherein one or more carbons are optionally replaced by 0, NR $^9$ , N $^+$ R $^9$ R $^{10}$ , S, S0, S02, S $^+$ R $^9$ R $^{10}$ , PR $^9$ , P $^+$ R $^9$ R $^{10}$ , phenylene, amino acid, peptide, polypeptide, carbohydrate, or polyalkyl.
- 157. A compound of claim 156, wherein  $R^{1}$ ,  $R^{10}$ , and  $R^{20}$  are independently selected from the group consisting of H and alkyl.
- 158. A compound of claim 157, wherein  $\mathbf{R}^1$ ,  $\mathbf{R}^{**}$ ,  $\mathbf{R}^{**}$  and  $\mathbf{R}^{**}$  are independently selected from the group consisting of H and  $\mathbf{OR}^{*}$ .

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159. A compound of claim 158, wherein R is H.

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- 160. A compound of claim 159, wherein R', R'', R', and R'' are each H.
- 161. A compound of claim 160, wherein d and e are independently 1 or 2.

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162. A compound of claim 161, having the formula:

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PEG = 3400 molecular weight polyethylene glycol polymer chain

163. A pharmaceutical composition comprising an anti-hyperlipidemic condition effective amount of a compound of formula (I) of claim 1, and

a pharmaceutically acceptable carrier.

164. A pharmaceutical composition comprising an anti-atherosclerotic effective amount of a compound of formula (I) of claim 1, and

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a pharmaceutically acceptable carrier.

165. A pharmaceutical composition comprising an anti-hypercholerterolemia effective amount of a compound of formula (1) of claim 1, and

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a pharmaceutically acceptable carrier.

166. A method for the prophylaxis or treatment of a hyperlipidemic condition comprising administering to

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a patient in need thereof a composition of claim 164 in unit dosage form.

167. A method for the prophylaxis or treatment of an atherosclerotic condition comprising administering to a patient in need thereof a composition of claim 165 in unit dosage form.

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168. A method for the prophylaxis or treatment of hypercholerterolemia comprising administering to a patient in need thereof a composition of claim 166 in unit dosage form.

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